Foreword

Nephrology, Dialysis and Transplantation

Is there a need for another nephrology text? Certainly a number of excellent textbooks are available for nephrologists to look up in-depth information on the various topics in the field. The current treatise pursues a different purpose and incorporates a novel approach pioneered by Dustri-Verlag. The ring binder format allows removal of chapters to be carried to rounds or conferences, and replacement of individual chapters as the field progresses in one, but not necessarily all other topics covered by the book. This obviates the need to purchase every two to three years an entire new set of textbooks and allows ongoing and timely updating of individual topics as required. It was the goal of the editors to create a clinically oriented text providing the reader with concise, up-to-date information without lengthy historical perspectives and background information. The development of a CD should later complement this treatise by allowing more in-depth listings of detailed references, presentation of charts, graphs, photomicrographs, x-rays, etc. The current two volumes represent a well rounded first edition, which was made possible by the diligent and devoted input from the co-editors, Drs. B. Peter Sawaya, Mohamed H. Sayegh, and Raymond M. Hakim, with enormous help from Dr. Nuhad Ismail. The overall quality of this treatise was accomplished through excellent contributions of the authors of the individual chapters. The authors were recruited from around the world and the editors would like to extend their deepest gratitude to these fine academicians for their great work. We are looking forward to an ongoing collaboration in the continued updating process of the text. This lively process of continuous updating will hopefully be enhanced by input from the readers, which is solicited and welcomed by all section editors and the chief editor. Finally, we would be remiss if we did not express our thanks to Jörg Feistle of Dustri-Verlag, who has been a consistent and pleasant force essential to the creation of this work. Looking forward to an enjoyable and successful ongoing documentation of the clinical knowledge base and progress in the field of nephrology, dialysis and transplantation.

Hartmut H. Malluche
Lexington, July 1999

Diagnostic Evaluations of the Kidney and the Urinary Tract

Francis Dumler, Leslie L. Rocher and Beatrice L. Madrazo

Urinalysis

The urinalysis is the single most useful and cost effective method of screening for renal and urological disease. It is simple, inexpensive, widely available, and noninvasive. Although not specific as to cause, urinalysis provides valuable information regarding the type and severity of renal involvement. Until recently, it was common practice to perform a urinalysis on all patients upon hospital admission or for preoperative clearance regardless of clinical presentation. This is not cost effective, and routine urinalysis is no longer recommended as a screening test in the general population. However, it is indicated in all patients at risk or suspected of having renal or urological disease. In addition, pregnant women, diabetics, and the elderly should be routinely screened. In patients with proteinuria, urinary sediment findings are a general predictor of histology on renal biopsy.

Early morning concentrated urinary specimens are preferred for urinalysis. Optimal samples are obtained after 14 hours of no fluid intake. Specimens can be obtained by spontaneous voiding, catheterization, or suprapubic aspiration. Clean-catch/midstream-voided samples are first choice. In males, specimens should be obtained after retraction of the foreskin. Females should manually separate the labia and gently clean the periurethral area using cotton balls prepacked in a soap solution. Suprapubic aspiration is most suitable for infants and has almost no use in adult practice. Urinalysis is best performed within 2 hours of collection. If needed, samples may be maintained at 4°C for up to 24 hours. When delays are expected, adding a few drops of acetic acid facilitates the preservation of formed cast elements.

A sample of urine is placed in a clear tube for dipstick testing. A similar aliquot, usually 10 – 12 mL, is centrifuged at 3000 rpm for 3 – 5 minutes, the supernatant poured, and the sediment resuspended in the residual volume, usually 0.1 mL, for microscopic analysis. A complete urinalysis consists of 3 major evaluations: physical examination, overall chemical composition, and analysis of formed elements in the sediment. In many laboratories the latter is performed only if dipstick testing is abnormal or when specifically requested regardless of dipstick results.

Physical examination of the urine is done by visual inspection of the sample, placed in a clear transparent container, under proper lighting, and against a white background. The color of the urine is determined by its chemical composition, concentration of solutes, and pH. Hematuria is the most common cause of abnormal color, ranging from red to black depending on amount, pH, and time. Red-tinged urine may also be seen with hemoglo-

Table 1. Routine Urinalysis Testing by Dipstick

Parameter	Seconds	Comment
Glucose	30	No false positives
Bilirubin	30	Noncharted colors are positive*
Ketone	40	Detects acetoacetic acid only
Specific Gravity	45	Not affected by glucose or dye
Blood	60	Hemoglobin and myoglobin*
pH	60	
Protein	60	Albumin > globulin > light chains
Urobilinogen	60	
Nitrite	60	Positive test suggests >10^5 CFU/mL
Leukocytes	120	Fairly specific

*False negative results may occur due to high ascorbic acid content

binuria and myoglobinuria, after eating beets, and during rifampin therapy. Yellow to brown urine is due to bile pigments in jaundiced patients. Urine of normal color upon voiding that darkens with time suggests porphyria (porphobilinogen), melanoma (melanogen), or alkaptonuria (homogentisic acid) in the appropriate clinical setting. Many drugs also influence the color of urine. The urine sample may be immediately cloudy due to the presence of formed elements, or it may get cloudy later because of precipitation of phosphates (alkaline or neutral pH) or urates (acid pH). Refrigeration accelerates precipitation. Profuse white foam may suggest proteinuria. A pungent smell suggests bacteria, while a sweet fruity odor may be due to ketones. In addition, inborn errors of metabolism may lead to a particular smell in the urine: maple syrup (maple syrup urine disease), mousy (phenylketonuria), sweaty (isovaleric acidemia), or fishy (hypermethionemia) odor.

Overall chemical composition is most commonly evaluated using the dipstick method. Parameters usually tested are listed below and in Table 1 by the time required to complete the reaction.

Glucose: Measured using a specific glucose oxidase and peroxidase method. Glucose is metabolized with glucose oxidase into gluconic acid and hydrogen peroxide. The peroxidase catalyzes the oxidation of a potassium iodide chromogen by hydrogen peroxide resulting in a shade of colors ranging from green to brown. False negatives may occur in the presence of large amounts of ascorbic acid.

Bilirubin: Under normal circumstances only conjugated bilirubin is excreted into the urine. In patients with jaundice due to obstruction or hepatocellular disease, bile pigments overflow into the urine. Bilirubin binds to diazotized dichloroaniline in a strong acid medium and produces various shades of tan.

Ketone: The nitroprusside reaction, which detects acetoacetate, is most commonly used. Beta hydroxybutyric acid (which accounts for 80% of ketones in blood) and acetone are not detected by this method. With prolonged fasting or starvation, ketonuria may be detected in the absence of ketonemia.

Specific gravity: Assesses the ability to concentrate or dilute the urine. It correlates closely with osmolality except when a high concentration of glucose or other substances

present in the urine (i.e. contrast agents, proteins) contribute more mass (an increase in specific gravity) than osmols. The usual range is 1.001 – 1.035. It can be measured using a hygrometer, a refractometer, or a dipstick; the latter is most commonly used. The dipstick detection method uses a polyionic polymer reagent that releases hydrogen ion (H^+) as it is saturated with cations present in the urine. The resultant change in acidity of the indicator dye causes a color change from blue to yellow. Although not influenced by glucose or contrast agents, this method is useful only as a screening tool. It tends to overestimate specific gravity at pH < 6.0 and underestimate at pH > 7.0. When clinically relevant, it is essential to measure urine osmolality. Osmolality provides the true measure of solute concentration in the urine. It is usually quantitated by the freezing point technique. Normal values range from 50 to 1,200 mosm/kg.

Blood: Detection is based on the pseudoperoxidase capacity of hemoglobin or myoglobin to catalyze a reaction between diisopropylbenzene dihydroperioxide and 3,3',5,5'-tetramethylbenzidine. A spotted pattern indicates intact red blood cells, and a uniform pattern suggests free hemoglobin, myoglobinuria, or methemoglobinuria. This method is very sensitive and can detect as little as 3 red blood cells (RBC) per high power field (HPF). A positive test in the absence of RBCs in the urinary sediment usually implies lysis of RBCs with release of hemoglobin but may be due to the presence of free pigmenturia. Specific testing for hemoglobinuria or myoglobinuria should be ordered for definitive identification when clinically indicated.

pH: Although the normal range is from 4.5 to 7.9, the usual urinary pH is between 5.0 and 6.5. During waking hours urinary pH is lower as the acid load contained in the diet is excreted.

The most common detection method uses methyl red and bromothymol blue, to provide a wide range of colors for measuring pH. A consistently alkaline pH may be associated with a substantial vegetarian diet, the presence of urea-splitting bacteria, or metabolic alkalosis. An acid pH is common during large meat consumption but may be indicative of a metabolic acidosis. The dipstick technique is adequate for screening only. When acid-base disorders are clinically suspected and knowledge of the urine pH is essential for diagnosis and treatment, accurate measurement requires use of an electrode pH meter and a urine sample collected under oil.

Protein: Urine dipstick techniques for protein primarily detect albumin and do not react with immunoglobulin light chains. Sulfosalicylic acid detects both albumin and immunoglobulins. These techniques provide only a qualitative assessment. As proteinuria is the major abnormality observed in patients with renal disease, a positive dipstick test should be followed by quantitation of protein in a 24-hour urine sample, or at least by a protein to creatinine ratio in a random sample. Dipstick methods use a pH-sensitive colorimetric indicator, tetrabromophenol blue buffered at pH 3.0, that changes from yellow to dark green and turquoise as protein concentration increases. The color shift is caused by the binding of negatively charged proteins. Neutral or positively charged proteins will not cause color change. As little as 20 mg/dL of albumin can be detected. It may be difficult to differentiate normal from trace. A high urine pH may give a false negative result. Detection of proteinuria is the most important reason for ordering a urinalysis when screening the general population for the presence of renal disease.

Urobilinogen: Based on the reaction between p-diethylaminobenzaldehyde and a color enhancer that reacts with urobilinogen in a strong acid medium to produce a pink-red color. A value > 2.0 mg/dL marks the transi-

Table 2. Urinary Sediment: Normal Values and Clinical Significance

RBC: < 5/mm^3 or < 3/HPF (0.3 mm diameter)*	
WBC: < 10/mm^3 or < 5/HPF (0.3 mm diameter)**	
Tubular epithelial cells: usually distal tubular cells (< 1/HPF)	
Squamous epithelial cells: lower urinary tract	
Casts: distal tubular lumen molds of Tamm Horsfall matrix:	
hyaline:	no clinical significance
RBCs:	glomerular hematuria
white blood cells:	inflammation of renal parenchyma
epithelial cells:	desquamation of tubular epithelium
granular:	denatured cells, precipitated plasma proteins

*If >80% of RBCs are dysmorphic (with blebs or fragmented), the likelihood of glomerular hematuria is high
**Eosinophiluria (Hansel staining technique) is highly suggestive of allergic interstitial nephritis, particularly when infection or other causes of acute tubular necrosis are excluded

tion from normal to abnormal. A high urobilinogen concentration suggests the presence of a hemolytic process. As the base value is equivalent to 0.2 mg/dL, this test cannot determine the absence of urobilinogen.

Nitrate: Many urinary tract pathogens are capable of converting nitrates to nitrites. Dipstick methods allow nitrites to react with p-arsanilic acid to form a diazonium compound, which, after further reaction with 1,2,3,4-tetrahydrobenzo(h)-quinolin-3-ol, results in a pink end point. False negatives occur when low dietary protein intake results in a low nitrate content in the urine, when prolonged storage in the bladder leads to nitrite breakdown, or when high concentrations of ascorbic acid ($\geq$ 25 mg/dL) are present. In addition, gram-positive organisms do not break down nitrate. This test may be negative in up to 50% of patients with bacteriuria.

Leukocytes: Lysed white blood cells (WBC) will release esterases. Dipstick methods provide a substrate that liberates 3-hydroxy-5-phenyl pyrrole after hydrolysis. The pyrroles then react with a diazonium salt causing a change in color from pink to purple.

Microscopic examination of the urinary sediment is a very useful and semiquantitative procedure. A drop of resuspended urine is placed on a glass slide, shielded with a cover slip, and examined at low (100x – 160x) and high (400x) magnification under a bright-field microscope. Although not essential, some recommend use of a counting (Fuchs-Rosenthal) chamber. Timed collections (Addis counts) are rarely used because they are cumbersome, formed elements deteriorate, and other diagnostic methods, such as renal biopsy, are more likely to provide a definitive diagnosis. Phase-contrast microscopy enhances cell morphology and allows the best definition of all formed urinary sediment elements. Polarized light may be used to look for anisotropic crystals (as is done with synovial fluid in the assessment of crystal-induced arthropathy). In general, the sample should be examined as soon as possible to avoid bacterial contamination and lysis of formed elements. Normal values for the urinary sediment are shown in Table 2.

Red blood cells (Figure 1a): The normal amount in a spun urinary sediment is < 3

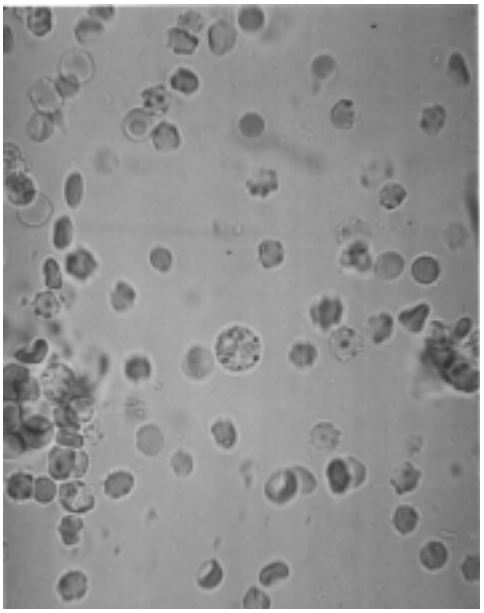
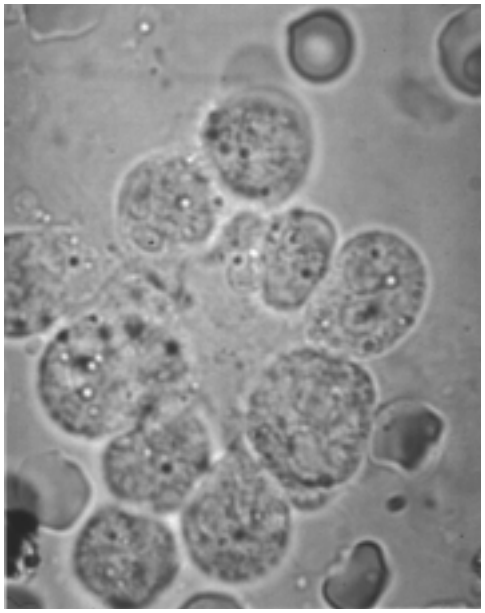


Figure 1a.



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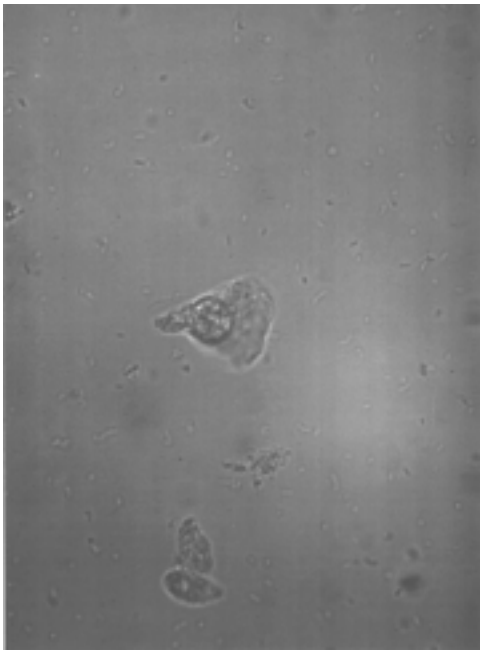

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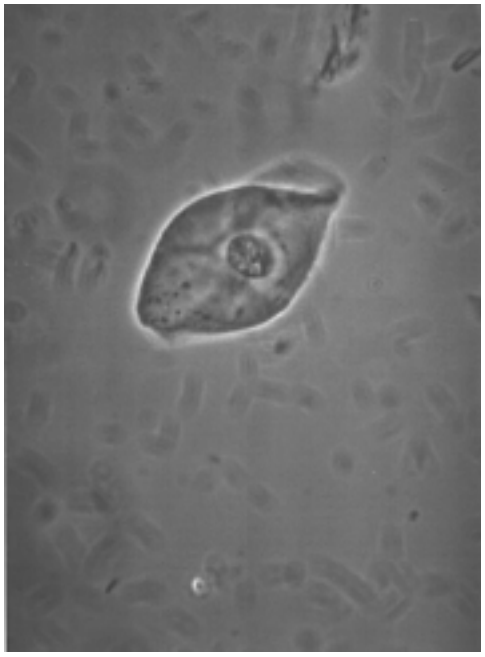


Figure 1d.

Figure 1. Urinary sediment cells. a: numerous RBCs and occasional white (granular) cells; b: numerous white cells in cluster and occasional RBCs; c: tubular epithelial cells; d: transitional cells (with permission of Hoffmann-La Roche Inc., copyright 1973)

RBCs/HPF. Because of varying amounts of RBC sediment on centrifugation, some prefer to use a counting chamber and an aliquot of unspun urine. With this method the upper range of normal is 13,000 RBCs/mL. However, there are no data to substantiate a significant advantage relative to semiquantitative techniques. On occasion, yeast and air bubbles may be confused with erythrocytes. Adding a drop of 25% acetic acid will dissolve RBCs but not yeast or bubbles.

It may be clinically relevant to ascertain whether hematuria is glomerular, tubular, or distal to the renal papillae in origin. RBCs acquired distal to the renal papillae tend to be homogenous, while those originating from the glomerulus or tubuli are quite dysmorphic with various abnormalities in size, shape, and membrane appearance due to pH and osmolality changes in the distal segments of the nephron. The latter may appear as crenated forms, ghost cells, or biconcave disks, or may simulate budding yeast. Phase-contrast microscopy allows for the best discrimination between dysmorphic and homogenous (isomorphic) RBCs. All RBCs in normal urine are dysmorphic. Nondysmorphic hematuria is always abnormal. Hematuria associated with > 80% dysmorphic cells is very suggestive of glomerular disease. Furthermore, the presence of RBC casts or renal tubular epithelial cells containing phagocytized RBCs is almost always indicative of glomerulonephritis.

Although the above technique has potential for discriminating between glomerular (need for renal biopsy) and nonglomerular (need for urological workup) hematuria, patients with IgA nephropathy or postinfectious glomerulonephritis may have a predominance of nondysmorphic erythrocytes. In addition, aggressive diuresis with furosemide may convert hematuria from isomorphic to dysmorphic. Overall sensitivity and specificity values are 88% and 95%, respectively. Unfortunately, the negative predictive value is high enough that nonglomerular bleeding cannot be excluded by dysmorphic hematuria alone.

Perhaps the most important reason in testing for hematuria is the detection of urological malignancies. The US Preventive Services Task Force recommends screening all patients over age 60 for hematuria. In nonselected populations, the prevalence of hematuria is about 2 – 4%. Of those with a positive test, 1% are bound to have urological malignancies, the most common being bladder carcinoma.

White blood cells (Figure 1b): The normal amount in a spun urinary sediment is < 5 WBCs/HPF. Leukocytes are slightly larger than erythrocytes and have a granular cytoplasm. With the use of a counting chamber, the upper limit of normal is 2,000 WBCs/mL. Leukocytes may be differentiated from renal tubular cells by specific staining techniques or by addition of glacial acetic acid that enhances the nuclei of white blood cells. Leukocytes can enter the urine at any point in the urinary tract. The presence of white blood cell casts and proteinuria suggests nephron involvement. The most common causes of leukocyturia are infection, inflammation, hemorrhage, and contamination. Pyuria most commonly represents infection; its absence is helpful in excluding it. Polymorphonuclear cells (PMNs) are the rule. However, in acute allergic tubulointerstitial nephritis, a large number of urinary leukocytes are eosinophils; these are best identified using Hansel's stain (methylene blue and eosin Y in methanol). A positive value is defined by >5% of white cells. In addition to acute interstitial nephritis, eosinophiluria can occur in rapid (crescentic) acute glomerulonephritis (GN), acute prostatitis, and atheroembolic renovascular disease.

Renal tubular cells (Figure 1c): They are rarely detected in normal urine (normal ≤ 1 cell/HPF). They derive from the distal tubule, are slightly larger than leukocytes, and have a

single large round nucleus and granular cytoplasm. An increased number, when present, is indicative of tubular damage. They are better differentiated from WBCs by staining. When containing phagocytized lipid droplets, they are called oval-fat bodies. The identification of renal tubular cells containing phagocytized RBCs has the same clinical significance as an RBC cast.

Squamous epithelial cells: They are the most common cell types after white and red blood cells and appear as large flat cells which are derived from bladder, urethra, or vagina.

Transitional epithelial cells (Figure 1d): They line the urinary epithelium from the renal calyx to the proximal urethra. They are rarely present in normal urine but may be seen with infections and neoplasias of the urinary tract. When numerous, they are particularly suggestive of malignancy and require further cytologic examination.

Urinary casts are cylindrical elements formed in the distal tubule by aggregates of Tamm-Horsfall glycoprotein gel. This process is more likely to occur in acid urine at high solute concentration. Acellular casts may be hyaline, granular, waxy, or fatty. Cellular casts contain erythrocytes, leukocytes, or renal tubular cells. Pigmented casts may be observed in hemoglobinuria and in hyperbilirubinemic states. Casts should be screened for at low (10x) and identified at high (45x) power magnification. Large bizarre casts in males are likely of prostatic origin. Triamterene can form casts from trapped crystals at an acid pH.

Hyaline casts (Figure 2a): These are composed of Tamm-Horsfall glycoprotein and have a homogenous, clear, colorless appearance. They may be seen in normal individuals during high volume diuresis, in the course of febrile illnesses, or in concentrated urine. Their presence in the urine has no pathologic meaning.

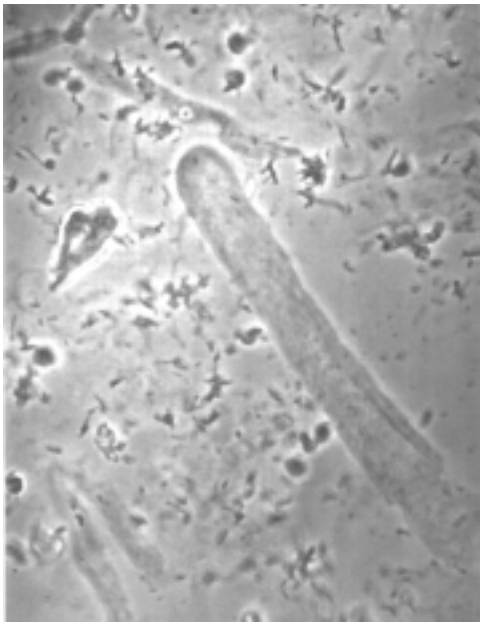
Granular casts: Finely granular casts, like hyaline casts, may be seen in normal individuals and provide little useful information. Coarse granular casts were thought to be the result of lysis of constituent granular cells. However, recent studies indicate that the granules are composed of plasma proteins incorporated into the Tamm-Horsfall glycoprotein matrix. Coarse granular casts are seen in a variety of glomerular and tubular disorders and are therefore not specific.

Waxy casts: They are highly refractile and, unlike hyaline casts, resistant to alkaline pH. They are broad and convoluted, not disease specific, and suggestive of tubular hypertrophy and chronic renal disease. They are believed to be the consequence of cellular cast degeneration and are usually seen with severe renal insufficiency.

Fatty casts: Usually seen in nephrotic patients. Oval fat bodies are tubular epithelial cells with lipid-laden drops commonly associated with fatty casts.

RBC casts (Figure 2b): They are characteristic of glomerular bleeding (glomerulonephritis), but on rare occasions may be due to severe acute interstitial nephritis. If the erythrocytes degrade, the structure takes the appearance of a pigmented cast. True hemoglobin casts are amorphous cylinders of an orange to reddish color. In acid urine, erythrocytes lose their hemoglobin, and the cast may look granular, but under phase-contrast the double contours of the cell membrane are clearly delineated. Disintegration of erythrocytes may eventually result in brick-red granular cast. Strings of RBCs are not truly casts but have the same clinical significance as a RBC cast.

WBC casts (Figure 2c): Indicative of infection (acute pyelonephritis), particularly when associated with bacterial casts. However, they may also be seen in acute and chronic intersti-



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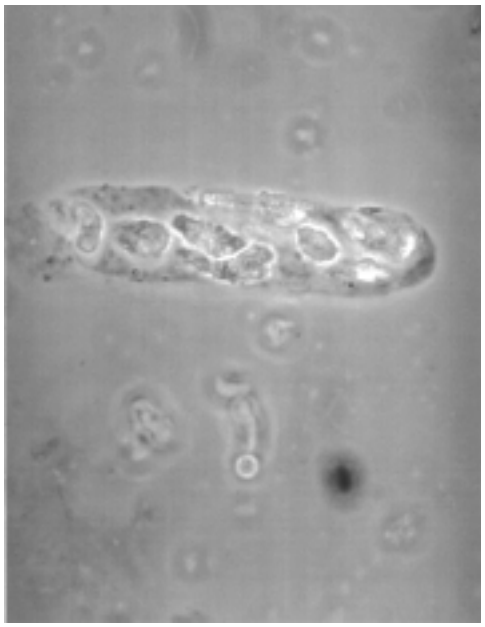

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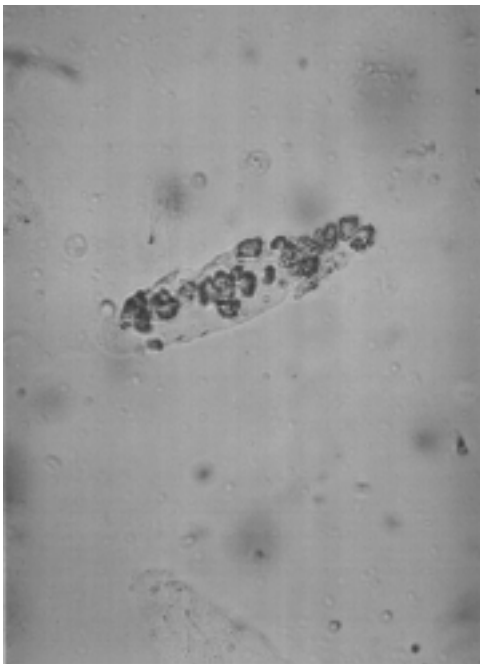

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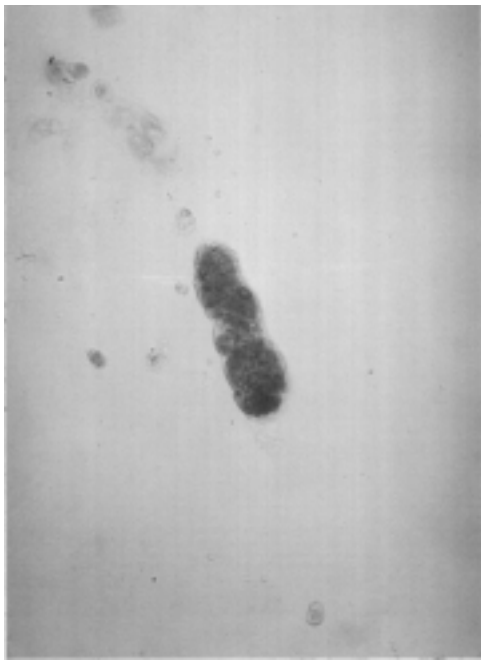


Figure 2d.

Figure 2. Urinary sediment casts. a: hyaline cast; b: tubular epithelial cell cast; c: white blood cell cast; d: RBC cast (with permission of Hoffmann-La Roche Inc., copyright 1973)

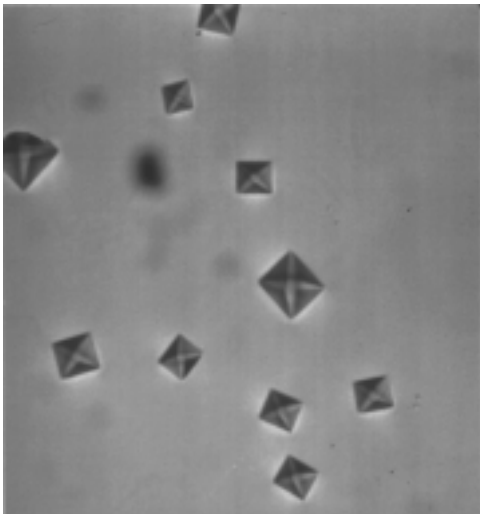
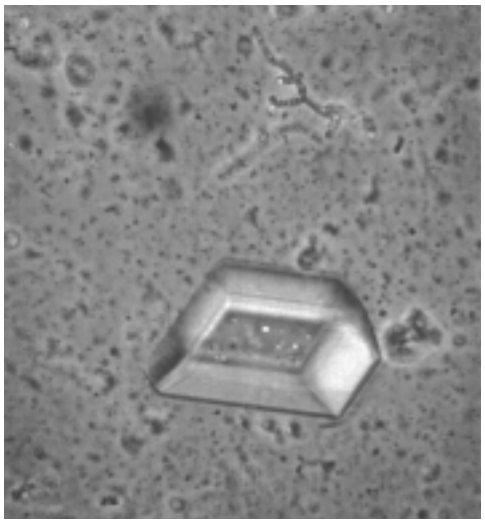


Figure 3a.



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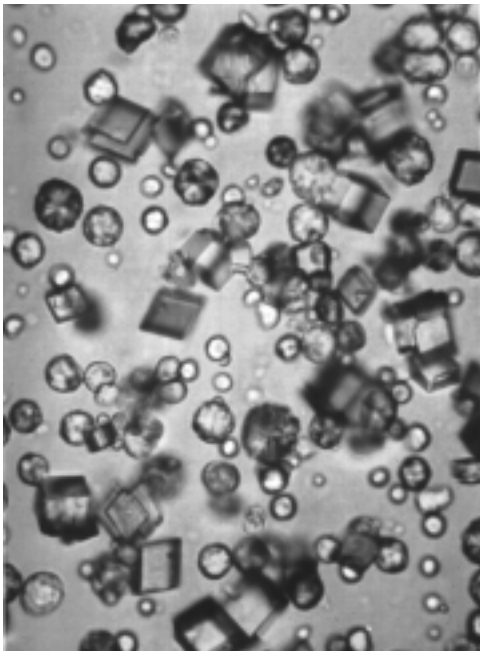

Figure 3c.

Figure 3d.

Figure 3. Urinary sediment crystals. a: calcium oxalate crystals (envelope forms); b: triple phosphate crystals (coffin lid forms); c: calcium carbonate crystals (rhombohedral forms); d: uric acid crystals (multiple forms) (with permission of Hoffmann-La Roche Inc., copyright 1973)

tial nephritis, postinfectious GN, and lupus nephritis.

Renal tubular epithelial cell casts (Figure 2d): They are formed of tightly packed nucleated cells and are indicative of tubular injury. They are usually seen in acute tubular necrosis (ATN) and acute GN.

A variety of crystals may be found in the urine (Figure 3a-d). Crystals of uric acid, calcium, phosphate, or urates are commonly found, in addition to amorphous phosphates and urates. In patients with active stone disease, larger quantities of crystals may be seen. None has specific clinical relevance, as their formation is pH, temperature, and food dependent. However, they may provide diagnostic clues in patients with microhematuria, nephrolithiasis, or toxin ingestion.

Urate: They may appear as an amorphous background in acid urine or have diamond, needle, or rhombus shapes, usually clustered like flowers. They are commonly observed and are not diagnostic. However, in the presence of acute renal failure (ARF), sheets of uric acid crystals are highly suggestive of acute urate nephropathy.

Amorphous phosphates: Common in alkaline urine, and can be cleared by addition of glacial acetic acid.

Calcium oxalate (Figure 3a): Octahedral envelope shapes are the best recognized. The presence of large amounts in a patient with ARF is strongly suggestive of ethylene glycol poisoning.

Triple phosphate (Figure 3b): Coffin lids or quartz crystals are the usual forms.

Cystine: Perfect hexagons ("benzene ring") are diagnostic of cystinuria.

In the absence of contamination, urinary lipids are almost always pathological. Lipiduria usually implies the presence of a nephrotic syndrome. However, it may occur in the absence of proteinuria in bone marrow and fat embolization syndromes. Numerous fat particles in urine may also be seen in preeclampsia and in rapidly progressive glomerulonephritis. Nonpolarizing fat particles seen within casts are called oval fat bodies. Maltese Cross spherulites are composed of cholesterol esters and are identified using polarized light. On bright microscopy they may be confused with RBCs.

Table 3. Urinalysis Findings in Various Renal Syndromes

Syndrome	Findings
– Glomerulonephritis	– hematuria with red blood cell casts – phagocytized red blood cells – dysmorphic red blood cells – proteinuria – lipiduria
– Acute tubular necrosis	– granular and epithelial cell casts – many epithelial cells
– Acute tubulo-interstitial nephritis	– pyuria with white and granular cell casts
– Acute pyelonephritis	– bacterial casts
– Urinary tract infection	– pyuria alone
– Prerenal azotemia – Obstructive uropathy – Renal ischemia	– near normal urine

The presence of microorganisms is most commonly due to contamination. The presence of leukocytes suggests infection. *Trichomonas vaginalis* is the most common protozoan in urine. *Enterobius vermicularis* is usually an anal contaminant. Parasites are not common except in specific endemic areas (*Schistosoma haematobium* in Africa and the Middle East).

Finally, automated urinalysis devices are being tested that can read dipstick strips and

examine the sediment using thin layers of uncentrifuged urine, a stroboscopic lamp, and a video camera. To recapitulate, from a clinical perspective a variety of renal syndromes can be associated with urine abnormalities that, although not specific, provide useful diagnostic clues (Table 3).

Clinical Evaluation of Renal Function

Glomerular Filtration Rate (GFR)

Glomerular filtration is a key function of the kidney. About 1.2 – 1.3 million glomeruli provide 1.0 m^2 of filtration surface and generate 180 L of tubular fluid per day. Glomerular filtration is the result of high hydraulic pressure across the glomerular capillaries and increased glomerular capillary hydraulic permeability. The glomerular filtration barrier is size and charge selective, with substances up to 10 kilodaltons (kD) being freely filtered. Approximately one-fifth of the cardiac output flows through the kidneys (500 mL/min per kidney). The rate of glomerular filtration is a function of renal plasma flow, hydrostatic pressure, oncotic pressure, surface area, and hydraulic permeability. In the absence of experimental data, filtration disequilibrium in humans is presumed from network thermodynamic and mathematical modeling. GFR and renal plasma flow remain constant when renal arterial pressure is varied between 80 and 180 mm Hg. This autoregulation phenomenon is achieved by corresponding changes in renal resistance vessels (afferent at normal pressures and afferent/efferent at low pressures) that ensure maintenance of adequate filtration pressure.

The concept of renal clearance is based on the premise that the excretion rate of any inert solute in the urine equals its simultaneous rate of removal from plasma. Therefore, the renal clearance (C) of a given substance is defined by the relationship between the excretion per unit time (U) and the concentration in plasma (P) as expressed by the relationship

$$C = U/P$$

True GFR is measured with a marker that is completely filtered and not reabsorbed, secreted, or metabolized. Inulin, a polymer of fructose (5.2 kD), is such a marker and has been long considered the gold standard. However, it is scarce, and the required technique is cumbersome and time consuming. Patients are typically studied in the morning after an overnight fast. An oral water load of 10 – 15 mL/kg is given followed by additional fluid intake to achieve urine flow rates of 4 mL/min. A loading dose of inulin is administered followed by a continuous infusion. Once a steady state has been reached (30 min), urine collections are obtained. Clearance is calculated using the time average inulin plasma concentration and the urinary excretion rate. The average of 3 – 4 clearance periods is used as the final calculation. Because glucose is detected in most inulin assays, it must be removed or measured and subtracted from the total plasma value. In a given individual, GFR measured by this technique is very constant, with a coefficient of variation < 10%.

Methods using noninulin labeled agents are discussed in the radionuclide section. Unlabeled radiocontrast agents such as iothalamate and diatrizoate meglumine have been used in lieu of inulin. As little as 1 mL injected subcutaneously is all that is required. However, assays require high performance liquid chromatography (HPLC), which is less easily available and more costly. An alternative method based on detection of low concentra-

tions of iodine can be used with the low-osmolality, nonionic radiocontrast agent iohexol.

There is a diurnal variation in GFR related to feeding. Values are highest in the afternoon and lowest at past midnight. Similar increases have been noted in patients receiving parenteral hyperalimentation, in patients with extensive burns, and during pregnancy when GFR may increase by as much as 50%. On the other hand, exercise induces transient decreases with up to 40% reductions after strenuous physical activity. During the first weeks of life, GFR is about 50% of normal but gradually rises to peak values by 12 months of age and remains constant up to age 40. A gradual decline is then observed, so that by the eighth decade GFR may be only at 30% of its peak value.

GFR measurements are best suited for monitoring disease progression in a given individual. Normal values have too wide a range to be useful in the detection or diagnosis of specific disease processes. Because renal size (and presumed filtration surface) is proportional to surface area, attempts have been made to normalize glomerular filtration values to this parameter. Although this approach tightens the distribution of normal values, the range is still substantial. Some of this normal variability could be minimized by measuring GFR at a fixed dietary protein intake.

Creatinine Clearance (C_{cr})

C_{cr} is the most widely used clinical estimate of GFR. Creatine is derived from the metabolism of creatine in skeletal muscle and from dietary meat intake, with about 1.6% of the creatine pool converted to creatinine. It is freely filtered at the glomerulus and not reabsorbed or metabolized. However, approximately 15% of the urinary creatinine is derived from tubular secretion. Its overall excretion rate is 15 – 20 mg/kg/day in females and 20 – 25 mg/kg/day in males.

Although creatinine generation is fairly constant at a given protein intake, several factors influence the apparent generation rate. Ingestion of cooked stewed meats increases the dietary creatinine load and the apparent generation rate. A change in muscle mass results in unstable creatinine generation rates that can take up to 3 weeks to stabilize. Similarly, a change in dietary protein intake induces changes in creatinine generation rate that do not reach steady state for up to 4 weeks. In addition, creatinine excretion is not constant over time. Short-term variations in a single individual range from 6 – 20%. As renal failure progresses, creatinine secretion into the gut and bacteria breakdown account for an approximate C_{cr} of 2 mL/min. Furthermore, tubular secretion of creatinine increases proportionally to the decline in GFR and may reach values 25% greater than at normal renal function. In severe renal failure, C_{cr} rates may be double those obtained with inulin. Incomplete urine collections are also an important source of error. It is best to use 24-hour collections to minimize the impact of bladder emptying and inaccurate timing.

Serum creatinine is usually measured using the Jaffé reaction (creatinine reacting with alkaline picrate) to form an orange-red complex. Unfortunately, this reaction also detects noncreatinine chromogens and therefore overestimates creatinine concentration. This is particularly true at low creatinine concentrations. Enzymatic methods are more precise, and HPLC provides direct measurements without any interference. The latter methods are more expensive and involved and are not frequently used in routine clinical testing.

Interestingly, measurements of C_{cr} using the Jaffé method in normal subjects yield results very close to the inulin clearance. The

Table 4. Empiric Estimation of Creatinine Clearance

Method	Formulae
1 Cockcroft, Gault [1976]	$\frac{140 - \text{Age (years)} \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}}$ Use 85% of value if female
2 Siersbaek, Nielsen [1971]	$\frac{19.653 - 0.142 \times \text{Age (years)} \times \text{Body Weight (kg)}}{10 \times \text{Serum Creatinine (mg/dL)}}$
3 Jelliffe [1972]	$\frac{\text{Body Weight (kg)} \times 146\text{-Age (years)}}{72 \times \text{Serum Creatinine (mg/dL)}}$ Use 90% of value if female
4 Gates [1985] (mL/min/1.73m^2)*	$0.5 + [89.4 \times \text{Serum Creatinine}^{-1.2}] + [55 - \text{Age (years)}] \times 0.005 \times 89.4 \times \text{Serum Creatinine}^{-1.2}]$ in males $0.5 + [60.0 \times \text{Serum Creatinine}^{-1.1}] + [56 - \text{Age (years)}] \times 0.005 \times 89.4 \times \text{Serum Creatinine}^{-1.1}]$ in females
*Body Surface Area (m^2)	$\frac{\text{Weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 71.84}{10000}$

1 Cockcroft DW, Gault MH 1976 Nephron 16: 31-41, 2 Siersbaek-Nielsen K, Molholm HJ, Kampan J et al. 1971 Lancet 1: 1133-1134, 3 Jelliffe RW, Jelliffe SM 1972 Mathematical Biosciences 14: 17-24, 4 Gates GF 1985 Am J Kidney Dis 5: 199-205

reason is that the overestimation of serum creatinine concentration due to detection of nonchromogens mathematically offsets the tubular secretion of creatinine. However, in renal failure the nonchromogen effect decreases as the serum creatinine concentration rises, and tubular secretion increases so that overestimation of GFR becomes the norm. Under these circumstances, inhibition of tubular secretion of creatinine with cimetidine results in values closer to those obtained with inulin clearance. Other drugs capable of inhibiting tubular secretion of creatinine include potassium-sparing diuretics, probenecid, and trimethoprim. In advanced renal failure (< 15 mL/min) the increased tubular reabsorption of filtered urea and the increased tubular secretion of creatinine balance each other, so that the average of the urea and creatinine clearances is very close to true GFR measured by inulin clearance.

In spite of the above limitations, C_{cr} measurements are very helpful in defining whether GFR is normal or abnormal and in determining whether it is stable or unstable over time. When urine collections are not available or are unreliable, indirect calculations of C_{cr} can be made using empiric formulae that estimate creatinine generation. A summary of these empiric equations is shown in Table 4.

Serum Creatinine and Blood Urea Nitrogen Concentration

Serum creatinine and blood urea nitrogen (BUN) concentrations are most commonly used as estimates of GFR because of ease of use, wide availability, and considerable practical value in patient care. Serum creatinine concentration is the recommended test for screening asymptomatic adults for overt renal dysfunction. However, the sensitivity for detecting mild decreases in true (inulin) GFR (50 – 90 mL/min) is not very high. Among patients with decreased renal function documented by inulin clearance, 25% have a normal creatinine clearance and 40% have serum creatinine measurements within the normal range. This is particularly true in patients with low muscle mass and reduced creatinine generation who maintain serum creatinine concentrations within the normal range despite a 25 – 30% loss of renal function. In addition, progressive renal injury may be associated with an increase in the tubular secretion of creatinine, so that the expected rise in serum creatinine concentration may be substantially blunted.

In most clinical circumstances, defining whether GFR is changing is more important than obtaining an accurate measure of the actual value. Serial assessment of serum creatinine concentration is very useful in this regard. Serum creatinine concentration varies inversely with GFR. In general, a rising serum creatinine concentration implies decreasing GFR, a falling serum creatinine concentration an increasing GFR, and a stable value no change. Nevertheless, there are certain limitations in using serum creatinine concentration alone as an index of change in GFR. In early renal disease GFR may fall substantially (by as much as 20 – 30%) without an obvious increase in serum creatinine. In addition, because the relationship between GFR and serum creatinine concentration is logarithmic, the absolute difference between creatinine measurements does not accurately portray the degree of renal deterioration. While a serum creatinine concentration increase from 1 – 2 mg/dL represents a 50% loss of function, the same increase in serum creatinine concentration at lower levels of renal function (i.e. from 4 – 5 mg/dL) implies a functional decline of a much smaller magnitude (20%).

Progressive renal failure can be monitored by a variety of methods, the most practical of which employs the reciprocal of serum creatinine concentration. In most patients with glomerular injury, reciprocal serum creatinine concentration values decline linearly with time as renal function worsens. This linear relationship may suggest that glomerular filtration changes at a constant rate throughout the course of disease. More likely, glomerular filtration decreases at a slower rate early on, only to accelerate late in the disease process. Although useful in patient management, this method is too insensitive for use in clinical research studies.

BUN concentration also varies inversely with the GFR. Urea (60 daltons) is the primary end point of protein metabolism. It is synthesized in the liver and distributed in all body fluids. It is freely filtered but reabsorbed in the proximal and distal tubules. However, it is not a very useful marker because its production and excretion rates are very dependent on dietary protein intake and proximal tubular reabsorption, respectively. Volume depletion from any cause enhances proximal tubular reabsorption of urea resulting in a disproportionate increase in BUN relative to the fall in GFR. This observation is used clinically to substantiate a diagnosis of prerenal azotemia. In addition, a high protein diet, increased tissue breakdown, and gastrointestinal bleeding will increase BUN concentration without a corresponding change in GFR. On the other

hand, alcoholism, liver disease, or a low dietary protein intake will lower BUN concentrations in the absence of changes in glomerular filtration. The usual BUN/Cr ratio is 10:1. Higher values indicate volume depletion, and lower values suggest volume expansion, liver dysfunction, or malnutrition. Urea clearance usually underestimates GFR and may be one half or less than that measured by creatinine or inulin techniques. However, in advanced renal failure (< 15 mL/min) the lower urea clearance (due to increased reabsorption) and the higher creatinine clearance (due to increased secretion) cancel each other so that the average of both is very close to the GFR measured with inulin.

Proteinuria

Proteinuria is the hallmark of many renal diseases. Substantial amounts of large molecular weight plasma proteins normally flow into the glomerular capillaries without crossing into the urinary space. The glomerular barrier with its charge and size selectivity prevents all but a small fraction of albumin, globulins, and other large proteins from entering the urinary space. Low molecular weight proteins (< 20 kD) are filtered freely but are then reabsorbed in the proximal tubule. Under usual circumstances, urinary protein excretion ranges between 30 – 130 mg/day, with the upper range of normal being 150 – 200 mg/day.

Approximately 60% of the total urinary protein excreted is derived from filtered plasma proteins. Of these, serum albumin is the single largest component (40%), followed by serum immunoglobulins (15%), and miscellaneous proteins including kappa and lambda chains (5%). The remaining 40% consists mostly of tubular proteins (Tamm-Horsfall protein or uromodulin) secreted into the urine. Uromodulin is a negatively-charged glycoprotein formed on the epithelial side of the thick ascending segment of the loop of Henle and the early distal convoluted tubule. Although small (80 dalton), it forms aggregates of $7 – 23 \times 10^6$ dalton. Its major physiological role is to bind and inactivate interleukin-1 and tumor necrosis factor. IgA and urokinase are also secreted by tubular cells and may appear in the urine in small amounts. Filtration of plasma proteins may increase with exercise, upright posture, or fever and may result in mild transient proteinuria.

Urinary protein content may be measured in random samples, in timed or untimed samples, and in 24-hour collections. The latter is the standard for assessing and quantitating proteinuria. The subject is instructed to discard the first voided morning urine, record the time, and collect all subsequent urine voided for 24 hours up to the time noted. When the urine is being evaluated for orthostatic proteinuria, the collection must be done in two separate containers, one for urine produced during waking hours (~16 hours) and the second for the overnight (~8 hours) sample. Urinary creatinine excretion rates may be used to gauge the completeness of the collection (20 – 25 mg/kg/day in males and 15 – 20 mg/kg/day in females). Because of the great variability of creatinine excretion, this approach is best used for longitudinal follow-up of proteinuria in a given patient. There are no specific recommended assays for measuring protein content in timed samples. The sulfosalycylic acid method relies on precipitation and measurement of turbidity with a photometer or nephelometer and has a 20% coefficient of variation. Trichloroacetic acid can be added to increase detection of gamma globulins. The Coomassie blue method is very reliable and is favored by many.

Urinary protein/creatinine ratios have been used as a surrogate of the 24-hour urinary protein method. Ratios >3.0 – 3.5 are seen with nephrotic range proteinuria, and ratios < 0.20 indicate values < 200 mg/day. Timing is important, as early morning samples tend to have less protein than afternoon samples. In addition, having to perform 2 measurements instead of one significantly increases the coefficient of variation for the test.

The normal urinary albumin excretion rate (microalbuminuria) is 12 μg/min or 20 mg/day. Its detection requires sensitive methods such as electrophoresis, immunoelectrophoresis, radioimmunoassay (RIA), immunoturbidimetry, laser nephelometry, or enzyme-linked immunosorbent assay (ELISA). The performance profile for these methods is similar, and selection usually depends on availability and local experience. Dipsticks for detection of microalbuminuria are now commercially available, but there is not enough experience with them to recommend routine clinical application. A timed 24-hour collection is the ideal method for sample collection. If not feasible, the second choice is a timed 30- to 45-minute collection after a 300mL water load. First morning sample testing should be used only by default.

The most important clinical use of urinary protein excretion measurements is the detection and monitoring of renal disease and its progression. In general, the use of standard protein determinations is sufficient for this purpose, and 24-hour collections are preferred over random sampling and protein/creatinine ratios. In patients suspected of having monoclonal gammopathies, specific tests are required for identification of light or heavy chains. In diabetic patients, testing for microalbuminuria is the method of choice for early detection of risk for nephropathy. In nondiabetic patients the relationship between proteinuria and progressive renal disease is significantly more variable than in diabetics. The number of false positive dipstick tests for protein in the population at large is relatively high, particularly when the expected prevalence of renal disease is low. For this reason, a positive test should be repeated and followed by stricter testing if positive. For instance, proteinuria detected by routine urinalysis in patients with lower urinary tract infections (UTI), fever, or congestive heart failure (CHF) may revert to negative upon improvement or correction of the underlying condition. In young, otherwise healthy individuals, proteinuria that is intermittent and postural (≤ 1,000 mg/day) has no pathologic significance. Renal survival of college students with intermittent proteinuria is the same as in normals.

Determining whether proteinuria is glomerular or tubular may have clinical relevance. An increase in both albumin and high molecular weight proteins indicates glomerular disease, whereas low molecular weight proteinuria suggests a tubular process. β_2-microglobulin is a small molecular weight (11.8 kD) protein that is freely filtered at the glomerulus and almost completely removed by proximal tubular cells, so that < 0.1% of the filtered load appears in the urine (370 μg/day). Many tubulointerstitial diseases are associated with a substantial increase in β_2-microglobulinuria, particularly acute pyelonephritis and acute interstitial nephritis. Defining whether glomerular proteinuria is selective or nonselective has been used in the past to differentiate minimal change disease from other causes of glomerular proteinuria. The amount of immunoglobulin G (IgG) (160 kD) is compared to that of albumin (69 kD) or transferrin (88 kD). A ratio < 0.10 is indicative of highly selective proteinuria (minimal change disease). A ratio > 0.50 is indicative of nonselectivity and suggests a diagnosis of glomerulonephritis.

Urinary Electrolytes

Measurement of urinary electrolytes may provide useful adjuvant clinical information. Under conditions of neutral balance, the 24-hour urinary sodium excretion is in equilibrium with intake and is a measure of dietary sodium. When balance is not neutral, it reflects either increased sodium reabsorption (decreased effective intravascular volume) or increased renal excretion (diuretics, salt-wasting). Urinary chloride measurements have a similar clinical implication. Urinary potassium excretion is a function of dietary intake, gastrointestinal losses, and renal excretion. In conditions associated with hypokalemia, a low potassium excretion is indicative of nonrenal losses (i.e. gastrointestinal tract), and a high excretion is characteristic of concomitant hyperaldosteronism (usually associated with a decreased effective intravascular volume) or renal potassium wasting (tubulointerstitial disease). In the presence of hyperkalemia, a low urinary potassium excretion denotes an inadequate renal response (decreased GFR, primary or secondary hypoaldosteronism), while a high value signifies an appropriate response and is suggestive of nonrenal causes of hyperkalemia. Quantitation of the urinary anion gap may provide an estimate of ammonia production and thus be useful in assessing the renal response in systemic hyperchloremic acidosis. Metabolic acidosis due to diarrhea is associated with increased ammonia production and a negative anion gap, while a positive anion gap indicates renal tubular acidosis (RTA). In most clinical circumstances urinary electrolytes are measured in random urine samples, so that concentrations rather than excretion rates are used for interpretation. These results are summarized in Table 5.

Other Tests of Tubular Function

Tests of concentrating ability: The most common cause of a decreased urinary concentration ability (hyposthenuria) is chronic renal failure (CRF), as a fall in concentration capacity parallels the loss in GFR. In tubulointerstitial or medullary diseases, the loss of concentrating ability may be greater than expected for the degree of renal failure. Central and nephrogenic diabetes insipidus are also causes of hyposthenuria. Urine osmolality (U_{osm}) is the standard assessment of concentrating ability. The early morning U_{osm} is > 800 mOsm/kg. A more rigorous evaluation requires induction of dehydration. An 18 – 26 hour water deprivation period (with a body weight loss of 3 – 5%) increases U_{osm} to about 1,100 mOsm/kg (range: 800 – 1400). When the test identifies a decreased urinary concentration, desmopressin acetate (DDAVP) may be used in a second phase to distinguish central from nephrogenic diabetes insipidus. Plasma arginine vasopressin levels may be measured concomitantly. The osmolal and free water clearance can be calculated using general renal clearance formulae as shown below:

$$\text{Osmolal Clearance } (C_{osm}) = \frac{\text{Urinary Osmolality } (U_{osm}) \times \text{Urine Volume } (V)}{\text{Plasma Osmolality } (P_{osm})} \quad (1)$$

$$\text{Water Clearance } (TcH_2O) = C_{osm} - V \quad (2)$$

(a negative value indicates net water loss or free water clearance).

Diluting capacity: This test is usually used for research purposes only. After a 1 – 2 L water load, while on a normal solute intake, healthy individuals dilute the urine to 40 – 80 mOsm/kg.

Hydrogen ion excretion: All measurements must be made using a pH meter in urine

Table 5. Clinical Interpretation of Urinary Electrolytes

Clinical syndrome	Urinary electrolytes
Hypokalemia	*Urinary K ≤ 30 mEq/L (extrarenal losses)*
– with associated metabolic acidosis:	Small bowel diarrhea, gastrointestinal fistulae, laxative abuse
– with normal acid-base parameters:	Low potassium intake, increased skin fluid losses, laxative abuse
– with associated metabolic alkalosis:	Colonic diarrhea, upper gastrointestinal losses. laxative abuse
	Urinary K > 30 mEq/L (renal losses)
– with associated metabolic acidosis:	Renal tubular acidosis, anion gap acidosis, ureteroneosigmoid-ostomy
– with normal acid-base parameters:	Recovering acute tubular necrosis, post obstructive diuresis, leukemia, magnesium depletion
– with associated metabolic alkalosis and low urinary chloride (< 20 mEq/L):	Vomiting, nasogastric drainage, chloride loosing diarrhea, prior diuretic use
– with associated metabolic alkalosis and high urinary chloride (> 20 mEq/L):	Diuretic use, Bartter syndrome, magnesium depletion if normo-tensive Hyperaldosteronism (primary or secondary), congenital adrenal hyperplasia, exogenous mineralocorticoid use, Liddle syndrome if hypertensive
Decreased total body water: (hypovolemia)	*Urinary Na ≤ 20 mEq/L (extrarenal losses)* *Urinary Na > 20 meq/L (renal losses)*
Increased total body water (hypervolemia/edema)	*Urinary Na ≤ 20 mEq/L*
	Decreased effective vascular volume due to congestive heart failure, liver disease, nephrotic syndrome
	Urinary Na > 20 meq/L Advanced renal failure
Metabolic alkalosis	*Urinary Cl ≤ 20 mEq/L* chloride responsive alkalosis Gastric fluid loss, non-reabsorbable anion delivery, post diu-resis therapy, post hypercapnea, villous adenoma, congenital chloridorrhea
	Urinary Cl > 20 mEq/L Chloride unresponsive alkalosis
Urinary potassium ≤ 30 mEq/L	Laxative abuse or severe potassium depletion
Urinary potassium > 30 mEq/L	Bartter syndrome or diuretic abuse if normotensive Primary hyperaldosteronism or licorice abuse if hypertensive and with low plasma renin Secondary hyperaldosteronism if hypertensive and with high plasma renin, Cushing syndrome with high plasma cortisol

Table 6. Serologic Tests Used in the Diagnosis of Renal Disease

Diagnostic test	Clinical Condition
ANCA-c	Wegener's, vasculitis, rapidly progressive glomerulonephritis
ANCA-p	Pauci-immune rapidly progressive glomerulonephritis
Anti GBM antibody	Goodpasture syndrome, renal allograft in Alport syndrome
C4 normal/C3 decreased	Postinfectious glomerulonephritis
C4 and C3 decreased	Membranoproliferative glomerulonephritis types 1 and 2
C3 nephritogenic factor	Membranoproliferative glomerulonephritis type2 > type 1
Anti nuclear antibody > 160	Systemic lupus erythematosus
Anti double stranded DNA	Systemic lupus erythematosus
Anti single stranded DNA	Drug-induced systemic lupus erythematosus
Anti-Scl-70	Scleroderma, CREST syndrome
Cryoglobulins	Primary and secondary cryoglobulinemia
Serum proteins by immunodiffusion	Monoclonal gammopathies
Hepatitis B/C screen	Glomerulonephritides associated with hepatitis B/C infection

collected under oil. A pH < 5.3 in an early morning specimen excludes a defect in hydrogen ion secretion (type 1 or distal RTA). An acid load test with $CaCl_2$ may be used to identify milder defects. Type 2 (or proximal RTA) patients have resting acidosis and an alkaline urine, but generate an acid urine in response to an acid load when serum bicarbonate concentration falls below 16 – 20 mEq/L. In CRF, the most common cause of decreased hydrogen ion excretion is a decrease in ammonia production. Although urinary ammonia production is not routinely measured, it can be estimated by the urinary anion gap.

Serological Evaluation of Patients with Renal Disease

Serologic tests are useful in evaluating patients with systemic or primary renal diseases in which glomerular involvement is highly probable. Tests include a wide range of assays aimed at detecting etiologic agents with pathophysiological roles or surrogate markers of diseases that define renal involvement. Many of these assays do not have established international standards, so results must be referred to normal values specifically defined for a particular procedure used. Commonly used tests are shown in Table 6.

Antineutrophilic Cytoplasmic Antibody (ANCA)

Recognition of these antibodies has had a major impact in clinical practice. Their detection is associated with syndromes characterized by systemic or renal-limited segmental vasculitis and fibrinoid necrosis, and titers correlate reasonably well with severity of illness. Most of these autoantibodies are IgG, although some patients may have a predominant IgM or IgA type. They produce a diffuse cytoplasmic appearance when using formalin-fixed neutrophils. However, with etha-

nol fixation 2 distinct patterns are observed: cytoplasmic (C) and perinuclear (P). Over 95% of C-ANCA is directed to a 29 kD serine proteinase known as proteinase 3 (PR3), which appears to be identical to myeloblastin, azurophil granule protein (AGP7), and P29. P-ANCA is mostly directed against myeloperoxidase (MPO) but binds with other intracellular components including elastase, lactoferrin, and cathepsin G.

C-ANCA is most often associated with Wegener's granulomatosis, while P-ANCA is mostly associated with pauci-immune renal disease. In the presence of a clinical picture consistent with rapidly progressive GN, a renal biopsy is still recommended because there are some false positive ANCA results in patients with acute interstitial nephritis, lymphoma, *Mycobacterium bovis* infection, and human immunodeficiency virus (HIV) disease. About 95% of patients with rapidly progressive GN and pauci-immune findings will have a positive ANCA. Of these, about 60% have a peripheral pattern. Only 5% of patients with immune-complex glomerulonephritis will be positive. In addition, 10 – 30% of patients with antiglomerular basement membrane (anti-GBM) disease will also have a positive ANCA test. ANCA does not react with the noncollagenous domain of type 4 collagen, indicating true double disease rather than antibody cross reactivity.

Some laboratories still use standard immunofluorescence microscopy. In this case all serum with a P-ANCA pattern should also be tested for antinuclear antibodies (ANA) to exclude an ANA peripheral pattern. More recent methods employ radioimmunoassay (RIA) or ELISA techniques using purified proteins as substrate. Assays using granule extracts have a higher false positive rate. Patients with high IgA levels, particularly in association with Henoch-Schönlein purpura, may have false positive results. ANCA may also be positive, in the absence of renal involvement, in patients with ulcerative colitis, sclerosing cholangitis, Crohn's disease, and retrobulbar fibrosis.

Antiglomerular Basement Membrane (Anti-GBM) Antibody

Anti-GBM antibodies are directed against an epitope in the noncollagenous domain (NC1) of the alpha3 chain of type IV collagen. The most specific assays use purified intact type IV collagen as substrate. Most laboratories employ solid phase assays (RIA, ELISA, immunoblotting), which usually detect only IgG antibodies; on rare occasions antibodies are IgA. Indications for testing include the presence of rapidly progressive GN, pulmonary-renal syndrome, or unexplained hemoptysis. Approximately 60% of patients with anti-GBM disease have lung involvement. A kidney biopsy still plays a major role in the diagnosis of anti-GBM disease. A positive linear staining in the absence of anti-GBM antibodies occurs in diabetes mellitus (DM), focal segmental glomerulosclerosis (FSGS), and acute postinfectious GN. There is no correlation between anti-GBM titers and severity of clinical illness. However, serial titers may be used to monitor therapy. Plasma exchange is continued until titers are less than twice background. Patients awaiting transplantation should not undergo surgery until antibody levels are low or undetectable.

In patients with Alport's syndrome the reactive epitope may be absent in the GBM. After renal transplantation about 10 – 30% develop a positive linear immunofluorescence on biopsy. However, very few have detectable circulating anti-GBM antibodies. The allograft disease is usually benign, with only a very small subset actually developing rapidly progressive GN and renal failure.

Serum Complement Levels

The serum complement battery routinely includes assessment of CH50, C3, and C4 levels. CH50 is assayed by incubating serum samples with sheep RBCs sensitized with rabbit anti-red-blood-cell antibodies. One CH50 unit is defined as the amount required to lyse 50% of RBCs in the assay. A normal CH50 indicates that complements 1 – 9 are present, but is less sensitive in screening for C4 deficiency. A low CH50 identifies patients with hereditary or acquired deficiencies. C3 and C4 are measured by nephelometry or immunodiffusion. A normal value does not exclude complement activation as a pathogenetic mechanism, because hypocomplementemia occurs only when consumption exceeds production. A low complement may be associated with immune complex disease, chronic antigenemia, stabilization of C3 or C4 convertase by autoantibodies such as nephritic factors, decreased production of complement components, and isolated genetic deficiencies.

Complement levels should be measured when acute GN is suspected because the complement profile may aid in the differential diagnosis. For instance, acute postinfectious GN is characterized by a normal C4 and a low C3 that rapidly returns to normal. Membranoproliferative glomerulonephritis (MPGN) type 1 is associated with a persistent fall in both C3 and C4, while type 2 has a normal C4 and a persistently low C3. The C3 nephritogenic factor (C3NeF) is an IgG autoantibody directed against a neoantigen in the C3 convertase C3bBb (alternate pathway). It is found in patients with MPGN types 1 and 2 but is much more common in the latter. It is also detectable in individuals with partial lipodystrophy, regardless of the presence of GN. C4NeF is an autoantibody that stabilizes C4b2a convertase (classical pathway). It has been described in patients with systemic lupus erythematosus (SLE), MPGN type 1, acute postinfectious GN, and in various other forms of chronic GN. Atheromatous embolic renal failure is commonly associated with significant hypocomplementemia.

Antinuclear Antibodies

Many autoimmune disorders are associated with the presence of antinuclear antibodies (ANA). Some are fairly disease specific, but many are not. However, the prevalence of ANA types varies enough between disease processes so that pattern identification becomes useful in differential diagnosis.

The most common screening method is indirect immunofluorescence. There are 4 general patterns described: diffuse, speckled, nucleolar, and peripheral. The diffuse pattern is the most commonly observed (60%), followed by the speckled (30%). Approximately 3 – 4% of Caucasians develop a positive titer with increasing age. In addition, low titers (< 1 : 60) are common in many acute or chronic inflammatory conditions. A positive result should be followed by further testing when clinically indicated. Assays using molecularly cloned antigens give the most specific test results.

Perhaps the most common use for ANA testing in clinical nephrology is detection of renal involvement due to systemic lupus erythematodes (SLE). Screening testing usually identifies a homogenous pattern at titers >1 : 60. In general, absolute levels of ANA do not correlate well with clinical disease activity. The presence of anti-double-stranded DNA (anti-ds DNA) antibodies, which bind to epitopes in the double helical structure of DNA, are highly specific for SLE but are seen in only 60% of patients. The presence of anti Smith (Sm), anti ribonucleoprotein particles

(RNP) or anti-SSA/Ro antibodies also suggest SLE but are less sensitive. Anti-ssDNA antibodies are very characteristic of drug-induced SLE. Anti-Scl-70 antibodies are highly specific for scleroderma and the CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome. Anti-SSB/La/Ha antibodies are characteristic of Sjögren's syndrome.

Antiphospholipid Antibodies

Antiphospholipid antibodies are a heterogenous family of acquired circulating IgG antibodies that react with various anionic phospholipids including cardiolipin, phosphatidic acid, and phosphatidylcholine. They have the common property of inhibition phospholipid-dependent coagulation reactions in vitro and are often detected as a prolonged PTT. Clinically, their presence is highly associated with a thrombotic diathesis. Some clinicians consider them a risk factor for recurrent clotting of hemodialysis vascular accesses. The lupus anticoagulant testing is most specific for these antibodies. It is important to recognize that IgG and/or IgM anticardiolipin antibody titers do not necessarily parallel the anticoagulant activity in vitro. Of related interest, a primary antiphospholipid syndrome characterized by otherwise unexplained thrombosis in large arteries and veins has been associated with the presence of these antibodies.

Cryoglobulins

Cryoglobulins are abnormal immunoglobulins that precipitate in the cold and redissolve on rewarming to 37° C. They are very nonspecific and occur in a variety of disease processes, including autoimmune disorders, infections, lymphoproliferative disorders, vasculitis, and primary GN. Small amounts of cryoglobulins (< 80 ng/mL) may be detected in up to 38% of normal subjects. The sampling method is critical, and the syringe and needle must be warmed up for the blood draw. A high titer (> 1g/dL) is considered diagnostic. Three major types have been described. Type I has a single monoclonal component (IgG, IgM, IgA, light chain); type II is a monoclonal IgM directed against IgG; type III is a polyclonal IgM against IgG.

Cryoglobulinemia of any type or etiology may cause renal involvement; however, it is most common with type II. About 50% of patients have isolated hematuria/proteinuria, 20% develop a nephrotic syndrome, and another 20% present as an acute GN. Other systemic symptoms suggestive of cryoglobulinemia include recurrent palpable purpura, skin ulceration and necrosis, arthritis, Raynaud's phenomenon, liver abnormalities, and neurologic symptoms.

Streptococcal Serologies

Streptococcal serologies (ASO, anti-DNAase B, antihyalurodinase, antistreptokinase, anti-DNAase) are most commonly used in the evaluation of patients with acute GN in whom an infectious etiology is sought. However, a positive test for group A β-hemolytic streptococcus is only indicative of previous infection and does not confirm a diagnosis of postinfectious GN. These tests are positive in > 95% of patients with throat infection and 80% of patients with skin infections. Titers become positive within 1 – 5 weeks of infection and last for about 3 – 6 months. When patients are promptly treated with antibiotics, the antibody response can be abrogated.

Serum Protein Electrophoresis

Serum protein electrophoresis is most commonly used to assess monoclonal gammopathies. Standard serum protein electrophoresis does not identify light chains. Immunoelectrophoresis identifies both heavy (G, A, M, D, E) and light (kappa and lambda) chains. Immunofixation is a more reliable method. It is important to perform immunoelectrophoresis in both urine and plasma samples, as detection in urine but not serum is not uncommon.

Multiple myeloma and amyloidosis are the major renal diagnoses sought with these techniques. DM and SLE are associated with increased polyclonal urinary light chains. Monogammopathies may be seen in a variety of disorders, including hematologic, connective tissue, autoimmune, and dermatologic conditions. Actually, up to 3% of normal individuals over 70 may have an identifiable monoclonal component, usually < 3 g/dL. Of note, about 25% of patients with idiopathic monoclonal gammopathy eventually develop multiple myeloma.

Miscellaneous

Hepatitis B and C virus serology may be used for screening patients with glomerular disease that may be attributable to these agents. Periarteritis nodosa may also be associated with hepatitis B. HIV serology is indicated in patients suspected of having acquired immunodeficiency syndrome (AIDS) nephropathy. IgA levels are high in 30 – 40% of patients with IgA nephropathy.

Rheumatoid factor is an antibody with specificity for Fc fragments of IgG. The latex test is positive in 80% of patients with rheumatoid arthritis, and may also be positive in patients with subacute bacterial endocarditis, syphilis, tuberculosis, shunt nephritis, acute postinfectious GN, collagen vascular diseases, autoimmune diseases, and systemic vasculitis. An IgM rheumatoid factor is particularly common in Wegener's granulomatosis. An IgA rheumatoid factor is very suggestive of Henoch-Schönlein purpura.

Circulating immune complexes are measured using a C1q binding assay. They are positive in autoimmune, vasculitic, neoplastic, and infectious diseases. They have little practical application in clinical nephrology.

High serum IgE titers may be seen in Churg-Strauss vasculitis, allergic drug reactions, and in patients with latex allergy.

Renal Radiology

Intravenous Pyelography (IVP)

Radiologic techniques are based on the differential attenuation of X-rays by tissues. Dense structures such as bones greatly attenuate the beam and appear light on film. Low-density tissues like fat cause little attenuation and appear dark. High-osmolality contrast media (diatrizoic or iothalamic acid) are composed of a negatively-charged anion containing a benzene ring with 3 iodine molecules and a positively-charged cation (sodium or methylglucamine). Newer low-osmolality agents, anionic (ioxaglate-dimer) or nonanionic (iopamidol, iohexol, ioversol), provide twice the concentration of iodine for a given osmolality than conventional agents. Use of low-osmolality agents reduces the prevalence of side effects from 5 – 1%. Severe reactions including cardiac arrhythmias, cardiac arrest, pulmonary edema, loss of consciousness, and

seizures occur in < 0.01 of patients and are 5 – 10 times less common with the use of low-osmolality agents. Fluid restriction in preparation for an IVP is no longer warranted except to minimize emesis. Patients are asked to abstain from food after midnight and limit fluid intake to < 500 mL in the 4 hours preceding the study. A laxative such as bisacodyl may be used daily for 1 – 2 days prior to IVP.

The major clinical advantage of the IVP is its ability to provide an overall survey of the anatomy of the kidney and urinary tract as well as an estimate of renal function. A drip technique allows delivery of higher doses with less discomfort and may improve the nephrographic phase. The nephrogram defines renal size and contour and identifies changes in substance. The blush of contrast in the renal capillaries allows definition of the parenchyma, and, as it concentrates in the proximal collecting tubules (PCT), the image is enhanced. A normal nephrogram is synchronous and symmetrical; if not, the presence of nonfunctioning parenchyma should be considered. The left kidney is usually 2 cm longer than the right; a renal size < 11 cm is abnormal. Renal size by IVP is greater than by ultrasonography because of a greater magnification artifact and contrast-induced osmotic diuresis. Although resolution is 1.5 – 2.0 cm, a 1 cm cyst is easily observed whereas a 1.0 cm mass may not be apparent.

The pyelographic phase permits identification of abnormalities in the contour of the pyelocalyceal collecting system and recognition of intrapelvic filling defects. The ureters are not visualized symmetrically nor at the same time. Filling defects may also be noted. Persistent total filling of a ureter suggests an obstructive component. Retrograde and/or antegrade visualization may be required if there is concern about significant pathology. The bladder is well seen, but polyps or other lesions may be missed. Masses may appear as filling defects or as abnormalities in the contour itself. However, defects may be misinterpreted as superimposed bowel. Observed abnormalities may warrant further evaluation by cystoscopy. Small residual bladder volumes (< 50 mL) are not well seen. The urethra can be visualized by emptying the bladder post IVP. It should be specifically assessed with a voiding cystourethrogram or retrograde urethrography under special circumstances including bladder and/or perineal trauma, voiding abnormalities, and vesicoureteral reflux.

Major indications for IVP include acute renal colic and nonglomerular hematuria. In these conditions, IVP is more sensitive than ultrasonography because it provides anatomic definition of the entire urinary tract as well as functional information. Other clinical indications for IVP include renal stone disease, voiding difficulties, neurogenic bladder, recurrent urinary tract infections (UTIs), sterile pyuria, congenital abnormalities (Figure 4), unexplained abdominal pain, and postoperative complications (Table 7). With the advent of ultrasonography, computed tomography (CT), and nuclear imaging, IVP is no longer the first-line diagnostic study in patients suspected of having renal neoplasias, obstructive uropathy, or renovascular hypertension or in the follow-up of renal allograft recipients.

Renal tuberculosis is an important diagnosis to keep in mind. Pulmonary tuberculosis has decreased markedly but extrapulmonary disease has not changed in prevalence. Tuberculosis is more common in immigrant populations. A history of pulmonary tuberculosis is almost always present, but is usually inactive at the time of presentation. Renal lesions are indolent until very late in the course of disease. About 25% of patients have gross hematuria. Sterile pyuria is seen in about 10%. IVP is the test of choice and is positive in 90% of patients. Major findings include moth-eaten papilla, parenchymal calcification and

scarring, and multiple irregular infundibular stenosis or strictures with subsequent hydrocalicosis. If renal function is decreased (which happens about 50% of the time) then retrograde pyelography is indicated. If the ureteral orifice is scarred, cannulation may be very difficult. As the bladder is commonly affected, cystoscopy provides additional diagnostic benefit. Advanced disease may present as a nonfunctioning kidney (autonephrectomy).

Vesicoureteral reflux results from a dysfunctional vesicoureteral junction. If the intramural segment of the ureter is too short, the junction behaves as a leaky valve. As a child with this abnormality grows, the intraluminal segment lengthens and becomes fully operational. However, in some children this abnormality persists into adulthood. A diuretic intravenous pyelogram is very helpful in assessing this condition. Grade I reflux involves up to the lower third of the ureter. Grade II reaches the renal pelvis without causing dilation. Grade III results in mild pelvic dilatation. Grade IV produces marked dilatation and tortuosity of the ureter. At times, grade III may need to be differentiated from obstruction. Intrarenal reflux is more common in the upper and lower poles because these papillary orifices are round and more open. Patients with neurogenic bladder also have a higher incidence of reflux. When duplicate ureters are present, the lower one tends to reflux.

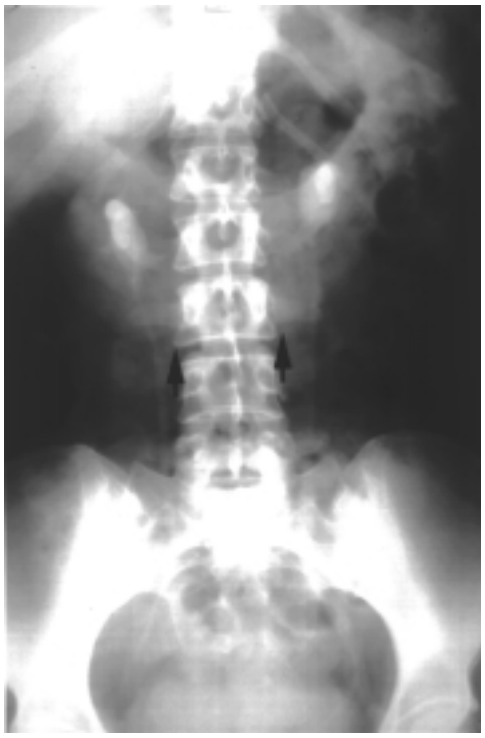

Figure 4. Horseshoe kidney. Excretory urogram demonstrates a medial orientation to the lower pole of both kidneys. The lower poles may be bridged by fibrous or nephrogenic tissue, such as in this case (arrows).

Ultrasonography

Ultrasonography is based on the differential acoustic impedance of tissues. Ultrasonic pulses are generated from short electric energizing pulses by a piezoelectric transducer. Bounced energy is reflected back to the transducer and reconverted to an electrical impulse. Transmission is optimal at water-like density; air and adipose tissue dampen the echo. Because the velocity of sound in tissues is constant, depth can be calculated from the time difference between sending and receiving an impulse. Real time digital images are generated by transforming reflected energy into a gray scale equivalent. Rapid sweeping with the transducer provides cross-sectional capabilities, and multiple planes can be sequentially generated by altering the positioning of the transducer. High-frequency probes provide better resolution but have less penetration. Patency of arteries and veins, as well as direction, magnitude, and velocity can be assessed with Doppler techniques. Renal ultrasonography is most often the first-line mo-

Table 7. Radiologic Studies Used in Diagnosis of Renal and Urological Disease

Suspected Condition	Radiographic Procedure	Comments
Nonglomerular hematuria Acute renal colic/nephrolithiasis Congenital malformations Recurrent urinary tract infections	IVP IVP IVP IVP	Anatomic definition of the entire urinary tract and estimation of individual function
Acute renal failure	US	Does not require contrast and is the best method to exclude obstruction
Chronic renal failure	US	Does not require contrast and increased echogenicity correlates with degree of sclerosis/fibrosis
Renal stone disease	US	Identifies stone only in the pelvis, may detect obstruction
Renal cysts	US	95% accuracy in differentiating cysts from solid masses US and CT are preferred for diagnosis of polycystic kidney disease
Renal masses	CT	Best method for assessing solid masses MRI is best for evaluating tumor extension into the renal vein and inferior vena cava and for identifying lesions < 2cm in diameter
Renal transplantation	US	Excludes obstruction, identifies perirenal fluid collections, provides supportive evidence of acute rejection
Perirenal hematoma	US	CT if recent hemorrhage is suspected
Atherosclerotic renal vascular disease & renal hypertension	DSA	Best resolution and the gold standard Spiral CT and MR angiography are promising Captopril renography is useful for screening
Renal vein thrombosis	MRA	Best resolution, US is a good alternative
Acute (complicated) pyelonephritis	CT	Can identify wedge lesions, abscess, and perirenal-fluid collection,US is a good alternative
Renal trauma	IVP	A normal IVP is highly accurate in excluding renal damage An abnormal IVP must be followed by dynamic CT with imaging of entire abdomen/pelvis

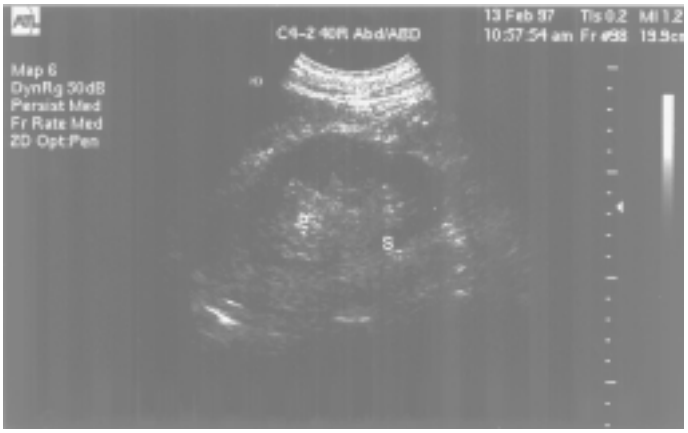

Figure 5. Normal kidney. Sagittal sonogram of the right kidney demonstrates the central hyperechoic sinus echo CT (S) surrounded by the hypoechoic renal parenchyma (P). The medullary pyramids are hypoechoic and located peripheral to the sinus (arrows).

dality for visualization of the kidneys. It is harmless, portable, free of ionizing radiation, and provides morphologic analysis totally independent of renal function.

The right kidney is best imaged with the patient in a supine position and with the liver as an acoustic window. The left kidney is best visualized in the right lateral decubitus position with the spleen as an acoustic window whenever possible. The echogenicity of the spleen is greater than that of the liver, which in turn is more echogenic than the kidney. If the ultrasonographic appearance of the liver is abnormal, comparisons may be distorted. Each kidney measures 10 – 12 cm in length. The renal sinus is hyperechoic. The renal pyramids are seen as hypoechoic triangles abutting the sinus and surrounded by the more echogenic parenchyma (Figure 5). The renal cortical area is homogenous. Minimal dilatation of the pelvis may be observed with a full bladder. Color Doppler technology allows sampling of the main renal vessels and its branches, including interlobar, arcuate, and capsular arteries.

Major strengths of ultrasonography include detection of pelvic and calyceal dilatation, identification of intrarenal fluid collections, separation of cystic and solid masses, and assessment of the perirenal space (Table 7). Disadvantages include poor resolution of the pelvicalyceal system and the retroperitoneum and poor visualization of the ureter. In addition, ultrasonography is very operator dependent.

Acute renal failure (ARF): Ultrasonography is the first diagnostic test of choice because it is the best method for excluding obstructive uropathy and does not require contrast administration. In hydronephrosis (Figure 6), branching, nonechoic, fluid-filled calyces, infundibulae, and pelvis distort the normal appearance of the compact sinus complex. Mild obstruction shows no distortion, and moderate obstruction is characterized by rounding of the collecting structures. In severe forms the sinus fat is replaced with rounded dilated infundibulae and calyces. Unilateral obstruction has multiple causes. Identification of bilateral hydronephrosis mandates assessment of the bladder and pelvis to exclude bladder outlet obstruction and retroperitoneal disease as etiologic factors. False negatives are unusual, but may be due to severe dehydration, acute obstruction with not enough time for distension, intermittent or partial obstruction, a ruptured calyx, staghorn calculi that obscure the underlying hydronephrosis, retroperitoneal fibrosis, tumor encasement, or near-absent renal function.

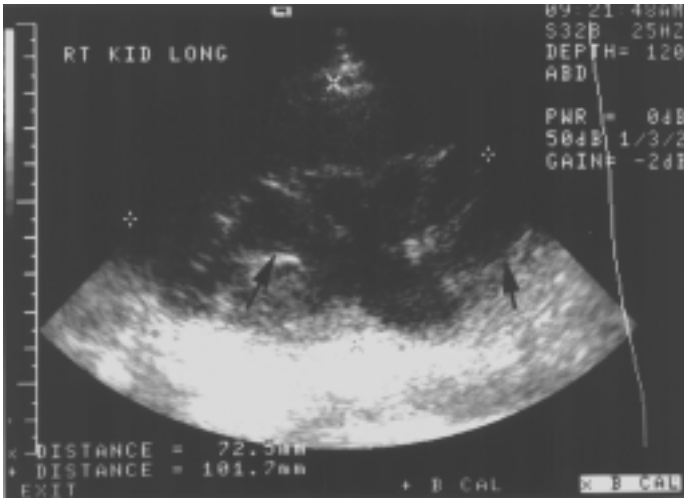

Figure 6. Hydronephrosis. The sinus echoes are separated by the hypoechoic urine-filled and dilated collecting system (arrows).

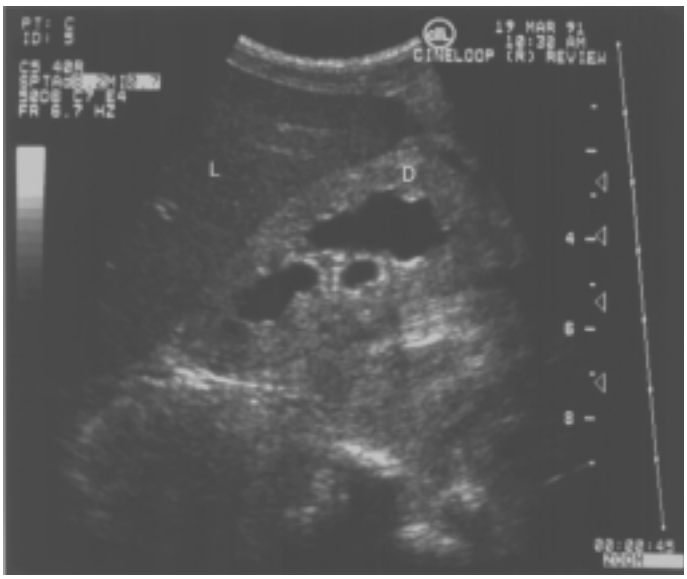

Figure 7. Medical renal disease. Sagittal sonogram reveals an echogenic renal parenchyma (D) with loss of normal central sinus echoes. The kidney is more echogenic than the liver (L).

Medical renal disease (Figure 7): Renal size, cortical thickness, and degree of echogenicity provide nonspecific information. Increased echogenicity is the most common characteristic associated with medical renal disease. There is a high degree of correlation between increased echogenicity and global glomerular sclerosis, tubular atrophy, and the presence of an infiltrative or inflammatory process.

Renal masses: The most common renal masses are cysts. Ultrasonography has a 94% accuracy in separating solid from cystic masses. About 90% of cysts are cortical and tubular in origin. It is not uncommon to find 1 – 5 cysts per kidney in patients over 50 years of age. Polycystic kidney disease (PKD) can be excluded if there are < 10 cysts per kidney set between normal-looking parenchyma. In PKD, other organs such as liver, pancreas, and

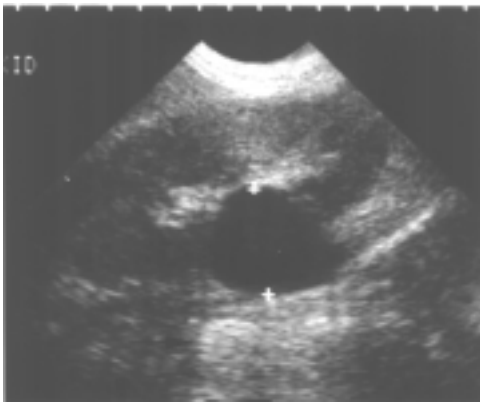

Figure 8. Renal cysts. A sharply circumscribed anechoic area consistent with a cyst is noted at the renal hilum. Acoustic enhancement beyond the cyst is present (arrow).

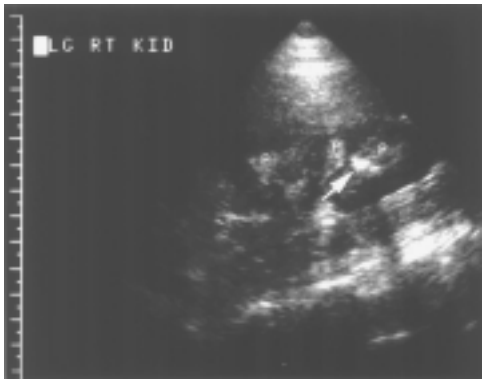

Figure 10. Medullary sponge kidney. The echogenic medullary pyramids create a pattern of triangular areas bordering the renal hilum (P). Note a large calculus in lower pole (arrow).

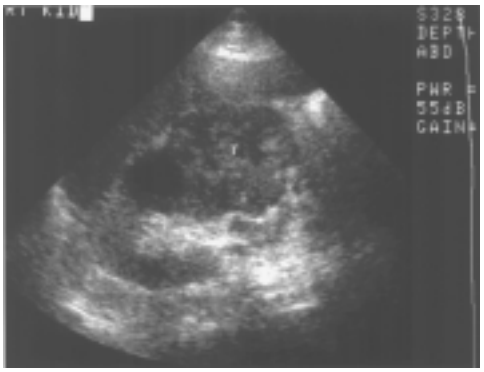

Figure 9. Renal cell carcinoma. Transverse sonogram demonstrates a large tumor (T) with small adjacent cyst. Obstruction of collecting system and/or infiltration of tubules by tumor gives rise to adjacent cysts (sentinel cyst).

spleen may show cystic lesions. Criteria for benign cysts include smooth and sharply defined walls, absence of internal echoes, posterior wall enhancement proportional to fluid content, and a narrow band of acoustic shadowing beyond the outer margin (Figure 8). If all these criteria are not met, CT is indicated. Bleeding into a cyst may give the appearance of a solid mass. Multiple thick septae are highly suggestive of malignancy. The best method for assessing solid renal masses is CT. Angiomyolipomas are benign tumors that are characteristically well circumscribed and very echogenic.

Malignant lesions are typically ≥ 3 cm in diameter before they are well detected by ultrasonography (Figure 9). About 85% of tumors are renal cell carcinomas. They are quite varied in appearance, with low, normal, or increased echogenicity. Posterior wall attenuation may be noted. Infiltrative tumors can appear as multiple hyperechoic masses in lymphomas and focal masses, as diffuse enlargement in leukemia, or as bizarre distortions. Renal cell carcinomas are best evaluated by CT and magnetic resonance (MRI).

Renal stone disease: When renal calculi is suspected, a kidney, ureter and bladder radiograph (KUB) should always be obtained first. Ultrasonography may detect actual calculi (> 5 mm in diameter) or identify hydronephrosis (Figure 10). Practically all stones regardless of composition are highly echogenic and accompanied by shadowing. Most stones cause obstruction at the level of the ureteropelvic or ureterovesical junction; neither area is well visualized by ultrasonography. IVP and/or CT may be required for definitive diagnosis.

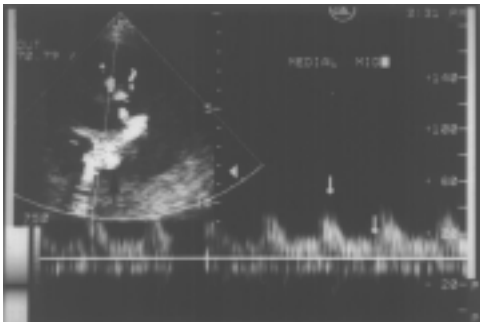

Figure 11. Normal renal transplant. Transverse sonogram demonstrates flow at the renal hilum (arrows). Spectral waveform on interlobar artery demonstrates normal low-resistance arterial waveform.

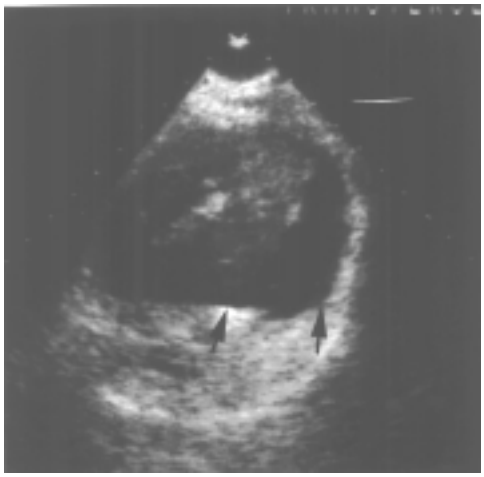

Figure 12. Renal transplant with infected lymphocele. Transverse sonogram of a left-sided allograft demonstrates a complex collection due to an infected lymphocele (arrows).

Infections: Ultrasonography is usually normal in about 75% of patients but may identify an underlying hydronephrosis. Acute pyelonephritis may result in renomegaly, heterogenous echogenicity, and perirenal fluid collections. A localized phlegmon presents as a focal, hypoechoic mass of ill-defined margins that may simulate a malignant lesion. A classic abscess has thick walls, well-defined borders, and a hypoechoic fluid level. Xanthogranulomatous pyelonephritis usually presents as enlarged hypoechoic areas surrounded by a hyperechogenic sinus.

Renal hypertension: Color Doppler ultrasonography is of limited value as a screening test. Intra-arterial digital subtraction angiography is the gold standard. Spiral CT angiography and magnetic resonance angiography show great promise. Captopril renography may be a useful screening tool.

Renal vein thrombosis: Magnetic resonance techniques are the best diagnostic tools. Ultrasonography with Doppler studies is a good alternate because it is noninvasive and requires no contrast administration. Findings include a dilated renal vein with a thrombus in the lumen, thrombus extension into the inferior vena cava, renal enlargement, thickening of Gerota fascia, and formation of pericapsular venous collaterals.

Renal transplantation (Figure 11): Ultrasonography is the method of choice for evaluation of renal allografts. Mild degrees of pyelocaliectasis are not uncommon. Urinomas, lymphoceles, hematomas, and abscesses are easily detected but have a similar appearance (Figure 12). Peripheral arterial resistance is usually quantitated as the resistivity index (RI).

$$RI = \frac{\text{peak systolic velocity} - \text{lowest diastolic velocitiy}}{\text{peak systolic velocity}}$$

A value > 0.70 indicates increased intrarenal resistance. This is a nonspecific finding commonly observed in acute rejection and cyclosporine nephrotoxicity but less frequently in delayed graft function. Acute rejection may also be associated with renal enlargement, prominent hypoechoic pyramids, and effacement of the central sinus. Acute allograft pyelonephritis is indistinguishable from acute rejection by ultrasonography.

Hematomas: Quite echogenic in the acute phase, hematomas become hypoechoic and septated as they liquefy. If recent hemorrhage is suspected, CT is indicated because ultrasonography cannot detect fresh blood.

Computed Tomography

CT is a digital cross-sectional imaging technique capable of detecting subtle variations in X-ray attenuation by different tissues. Data samples are obtained by moving the source around the patient at a given cross section of the body while measuring attenuation values along the X-ray beam. A computer calculates the average X-ray attenuation of all tissues within a specific volume element or voxel and represents it by a resulting number (CT number or pixel value). All CT numbers are referenced to water, which has a value of zero. Tissues less dense than water (fat) have a negative number; denser structures have positive numbers. Images are created by converting pixel values to light intensity on a cathode ray tube from which a hard copy (film) is obtained. Current scanners are capable of detecting a 0.3% difference in attenuation and achieving a spatial resolution of 0.5 – 1 mm. The system operator defines a window width (500 Hounsfield units [HU]) and an attenuation range (15 – 30 HU).

The attenuation coefficients within the retroperitoneum are different enough to allow visualization of the kidney, vascular structures, and the renal fascia. The renal parenchyma is uniformly homogeneous at 30 – 50 HU. The collecting system is differentiated from the parenchyma because of its water content (0 – 20 HU). Fat fills the perirenal space and sharply defines the renal border. Renal imaging by CT uses an initial digital/computer-generated radiograph to define the location of the kidneys. A nonenhanced study is then done using contiguous 1 cm thick sections. Thin sections (0.5 cm or less) are used occasionally to better delineate abnormalities or to identify small calculi. Contiguous bowel loops are identified by an oral barium swallow. Best definition is obtained with intravenous (IV) contrast media, except when calcification, hemorrhage, or urine extravasation is suspected, in which case a nonenhanced study is preferred. Images are usually displayed in the transverse plain, but sagittal and coronal images may also be constructed (Table 7).

The renal vascular anatomy is best seen with a bolus dye injection and rapid acquisition of images (dynamic CT). Within seconds the aorta, arteries, and veins are visualized. The nephrographic phase, characterized by enhancement of the cortex and the corticomedullary junction, is apparent within 1 min. The tubular phase, identified by increasing enhancement of the medulla, is noted at 2 min. Finally, the collecting system is apparent at 2 – 3 min. In patients with significant renal failure, enhancement is proportional to the amount of dye filtered, and usually only the vascular phase is reliably observed.

Obstructive uropathy: Ultrasonography is the technique of choice for initial evaluation of suspected obstructive uropathy. In addition to detection of hydronephrosis in a nonenhanced study, CT can define the anatomic site, degree, and cause of obstruction with nonenhancing imaging. Retroperitoneal fibrosis is suspected by increased attenuation within fat tissue that suggests encasement of the ureters. A dilated ureter is identified as a column of water surrounded by a thin tube. Extrinsic masses compressing the ureters, intraluminal masses, or stones may also be visualized. Regardless of composition, calculi have high attenuation rates (600 HU for calcium and 180 – 500 for uric acid) when compared to tissue (30 – 60 HU). Therefore, all uric acid and

cystine stones are radiopaque with CT. Blood clots have a wide range of HU ranging from soft tissue to near calculi. Serial examinations are required for better definition because clots lose attenuation with age.

Congenital anomalies: Usually found incidentally or by intravenous pyelography (IVP). CT does not provide any imaging advantage unless the kidney cannot be located or an identified mass needs further investigation.

Polycystic kidney disease: The kidneys are bilaterally enlarged with multiple cysts of various sizes distorting the collecting system. Hepatic, pancreatic, splenic, and pulmonary cysts may also be identified. Hemorrhagic cysts are seen as high-density lesions. Calculi within cysts and cyst wall calcifications may also be noted.

Acquired cystic disease: Multiple small cysts in hypotrophic kidneys may be seen in long-term dialysis patients. Perirenal hemorrhage and renal cell carcinoma are increased in this group.

Renal masses: Simple benign cysts are the most commonly detected renal masses, occurring in more than 50% of patients after age 50. They are characterized by a homogenous low attenuation value (0 – 20 HU) and nearly indiscernible thin walls, are very sharply delineated from the surrounding parenchyma, and are not enhanced by contrast. Diagnostic accuracy for simple cysts is virtually 100%. Parapelvic cysts are hilar renal masses with all the characteristics of simple cysts. They may mimic hydronephrosis or an extrarenal pelvis in nonenhanced scans.

Complicated cysts have a higher density, an irregular shape, and thickened or calcified walls. At times they may simulate solid tumors. Hyperdense lesions (50 – 90 HU) may be benign or malignant. The former include simple cysts complicated by hemorrhage, infection, dye leakage, and a high protein content. Lesions less than 3 cm in diameter and with simple cyst characteristics except for density are considered benign. Calcification always raises suspicion of malignancy. Occasionally, a benign cyst may show a small, fine, linear plaque. Septations in simple cysts are few in number and always less than 1 mm thick. When indicated, percutaneous cyst aspiration and biopsy may be performed under CT guidance.

Renal carcinoma accounts for 85% of primary renal malignancies. Approximately 1% are bilateral and 4.5% multifocal. Although most carcinomas are large at the time of diagnosis (7 – 8 cm), size alone should not be used as the major criterion for differential diagnosis. Renal cell carcinomas characteristically are > 3 cm in diameter, have a density greater than 30 HU but are less dense than the surrounding parenchyma, distort the renal contour, and are usually poorly differentiated from the rest of the parenchyma. They tend to be homogenous, but hemorrhage and necrosis may cause heterogeneity. Calcification may be present. CT is very useful for staging renal cell carcinomas: I – lesion limited to the parenchyma; II – extension to the perirenal space; III – extension to the renal vein, lymph nodes, or inferior vena cava; IV – extension outside Gerota fascia. Stages III and IV are better identified with CT than with angiography. Retroperitoneal lymph node involvement is well seen by CT. MRI is the technique of choice for evaluating tumor extension into the renal vein. Angiography is reserved for rare situations in which detailed vascular anatomy is needed. CT scanning is also an excellent method for detecting local recurrence after nephrectomy. A baseline study should be performed in the immediate postoperative period.

Metastatic renal disease is twice as common as renal cell carcinoma. Lung cancer is the most common type. Lesions look like renal cell carcinoma but are typically multifocal,

bilateral, small, and cortical in location. Renal vein and inferior vena cava involvement is rare in metastatic disease.

Lymphomas, particularly non-Hodgkins types, frequently involve the kidneys and are seen in 30 – 50% of autopsies. They usually appear as multiple bilateral nodules. A diffuse enlargement is due to progressive enlargement and coalescence of single lesions.

Angiomyolipomas are the most common benign renal tumors of the kidney. They are hamartomas in nature and usually present as a large solitary renal mass. Identification of adipose tissue within the mass virtually excludes malignancy. Hemorrhagic areas within the tumor are common. Tuberous sclerosis is associated with a high frequency of small, multiple, bilateral angiomyolipomas. Dynamic CT will usually demonstrate the hypervascular nature of the tumor.

Oncocytomas are benign tumors, usually 6 – 7 cm in diameter, that arise from the proximal tubular epithelium. They are solid homogenous masses of smooth contour, distinct interface, and, at times, a central stellate scar. Although these characteristics suggest a benign lesion, the diagnosis can only be confirmed histologically.

Transitional cell carcinomas account for 90% of renal pelvis neoplasms and are associated with exposure to organic chemicals used in aniline dye production. Papillary forms are most common (85%), tend to be low-grade, and are slow to infiltrate and metastasize. Nonpapillary lesions are more aggressive. Squamous cell carcinomas are the second most common type. They may be associated with infection and calculi in about 50% of patients. They usually present as an intraluminal mass of soft tissue attenuation (35 – 45 HU) with nodular borders, and they show enhancement with contrast. Large lesions may cause hydronephrosis. Calcification may occur, but it is less frequent than frank calculi. Loss of the peripelvic fat stripe indicates parenchymal invasion and overt malignancy. Because 40% of patients have concomitant pathology in the ureter or bladder, images including these areas are essential.

Pyelonephritis: CT is superior to ultrasonography for delineating renal and perirenal inflammatory masses. Findings range from a slight increase in overall renal size to radially oriented wedge-shaped areas of diminished attenuation oriented from the collecting system to the capsule. Focal renal enlargement with distortion of the renal contour may also be noted. A frank abscess will be delineated by a well-defined wall. The presence of gas within the renal parenchyma is highly suggestive of emphysematous pyelonephritis. Infected hydronephrosis (pyonephrosis) may show a debris-fluid level, gas, or both.

Xanthogranulomatous pyelonephritis may present as a focal tumefactive or a diffuse lesion. The parenchyma is replaced by masses that represent dilated calyces as well as abscesses filled with debris and pus. The thick walls noted are a result of granulation tissue and compressed normal parenchyma. Calculi are often lodged within the pelvis and calyces. Involvement of the perirenal and pararenal compartments is not uncommon.

Renal tuberculosis is second only to pulmonary disease. Most kidneys are small, with areas of focal fibrosis and distortion. Thickening of the pelvis and ureteric wall is very suggestive of tuberculosis. Calyces are usually filled with caseating material and putty-like calcifications or frank calculi.

Renal vascular disease: Infarcts are identified as wedge-shaped areas of diminished attenuation, with the cortical rim showing increased density due to perfusion from collaterals (Figures 13a and 13b). These lesions may also be seen in acute cortical necrosis, ATN, and renal vein thrombosis. Global in-

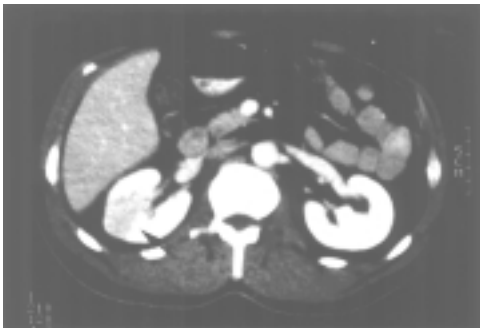

Figure 13a.

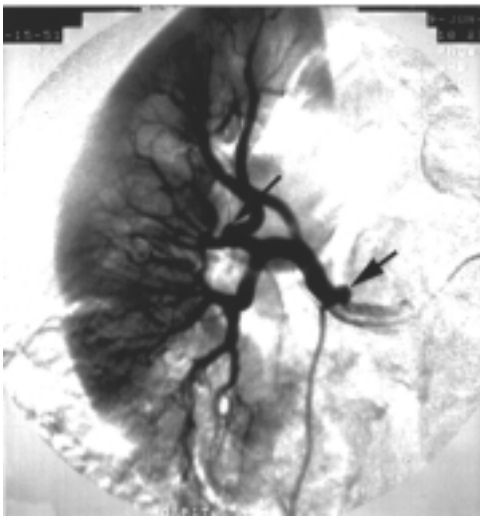

Figure 13b.

Figure 13. Renal infarction. a: Wedge-shape, low-density area is present in right kidney (arrow) in a 42-year-old male who presented with right flank pain and no evidence of bacteriuria. b: Renal arteriography shows 2 small renal aneurysms (arrows).

farcts produce a homogenous lesion involving at least 50% of the surface area. Acute renal cortical necrosis shows a thin rim of low attenuation between the capsule and the medulla. In renal vein thrombosis the kidney is enlarged and the renal vein full of low density material. Renal artery stenosis results in diffuse uniform atrophy of the parenchyma.

More recently, spiral CT has been used for noninvasive imaging of the vascular system. The kidneys are localized with standard nonenhanced CT. A dose of nonionic contrast medium is then injected manually and a short sequence of dynamic scans done for estimation of contrast transit time from the point of injection to the abdominal aorta. The spiral CT is then started at the level of the superior mesenteric artery after bolus injection administration and scans obtained at 2 – 3 mm section thickness with a table feed of 2 – 3 mm per second for a scanning time of up to 32 seconds. Multiplanar reformatting and 3-dimensional surface reconstructions are created by use of a threshold level dependent on the degree of vascular enhancement (130 – 220 HU). Maximum-intensity-projection images are reconstructed by eliminating bone structures from axial sections and subsequent display of the maximum pixel values along each path. Spiral CT can accurately identify multiple renal arteries and renal arterial stenosis in vessel segments between the origin and the hilum. More complicated anatomy requires use of active cine display of axial sections and multiplanar image reformatting at narrow intervals (1 – 2 mm) for evaluation of the entire vessel length. Spiral CT can detect mural calcification of blood vessels and acquires perfusion images (nephrographic phase) not available with magnetic resonance angiography. Potential difficulties with this technique include a relatively large dye load and difficulty in assessing peripheral stenoses and differentiating high-grade stenosis from total occlusion with collateral circulation. The overall specificity and sensitivity of this technique compared to angiography are 92% and 83%, respectively. The major clinical use of spiral CT is in the diagnosis of renal artery stenosis and in the anatomical assessment of living renal allograft donors.

Renal trauma: Best assessed initially by IVP. A normal IVP is highly accurate in excluding renal damage. However, an abnormal

IVP is nonspecific so that further examination by dynamic CT is indicated. Imaging of the entire abdomen and retroperitoneum is needed because about 20% of patients have other organs affected. CT scanning differentiates between minor (contusion, incomplete laceration, intrarenal hematoma) and major (complete laceration, renal fracture, shattered kidney) injuries. CT also identifies areas of focal renal infarction and subcapsular, perirenal, and pararenal hematomas as well as minimal amounts of bleeding (Figure 14). Accumulation of contrast-laden urine within the interstitial space of the kidney is characteristic of renal contusion. Parenchymal tears are seen as hypodense areas. If functional, they will be enhanced during dynamic CT. Focal infarctions are wedge shaped. Hematomas in the space medial to the kidney should raise suspicion of vascular damage. Arteriography is the procedure of choice for evaluation of potential vascular lesions.

Renal allograft evaluation: The major disadvantage when compared to ultrasonography is the need for a contrast agent. When hydronephrosis is present, CT may provide an etiologic diagnosis. Urinomas can be identified by assessing tissue density before and after dye injection. Acute rejection is characterized by loss of corticomedullary junction during dynamic CT.

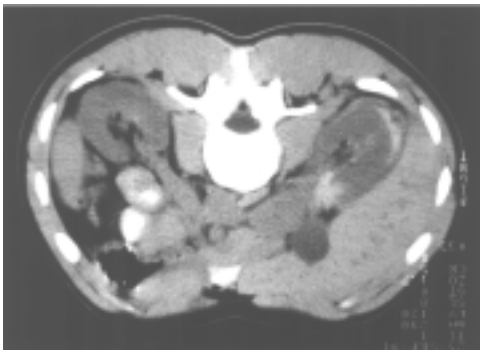

Figure 14. Renal trauma. Precontrast CT reveals a hyperdense perinephric collection secondary to hemorrhage (H)

Magnetic Resonance Imaging

MRI is based on the spontaneous alignment of magnetic moments of the nuclei contained in tissues when an external electromagnetic field is applied. Because H^+ is abundant in the human body and has a high gyromagnetic ratio, MRI is almost exclusively carried out with protons. Images are produced by applying multiple radiofrequency signals (256 – 512 pulses) over several minutes. Fat saturation spin echo techniques improve image resolution by reducing the respiratory artifact caused by moving subcutaneous fat.

Although CT is superior for defining calcified and fatty structures, MRI provides better tissue contrast resolution, does not require dye, directly measures multiplanar images, and has no biological side effects. Major drawbacks include availability, cost, and the relatively long time needed for imaging. MRI is most commonly used as a problem-solving technique when ultrasonography and CT provide equivocal results. The renal venous circulation is particularly well defined, and MRI is the technique of choice for detection of renal vein thrombus or tumor invasion (Table 7). Gadolinium is approved for use as a paramagnetic contrast agent. Minor side effects occur in 2.4% of patients (nausea, vomiting, urticaria). Only 5% of the usual iodinated dosage is delivered. Estimated incidence for anaphylaxis is 0.001%. No renal, hepatic, or cardiovascular toxicity has been reported.

Magnetic resonance angiography (MRA) is based on the phase differences between moving and stationary objects and on the bulk spin flow in the area of interest. Renal arteries are best studied with phase contrast and the renal

veins and inferior vena cava with time of flight techniques (TOF). Proximal lesions are better seen than distal or intrarenal ones, particularly limiting the study of fibromuscular dysplasia.

Magnetic resonance spectroscopy (MRS) requires use of a magnet capable of delivering at least 1.5T with a field homogeneity 100 times greater than for MRI. Nuclei used for spectroscopy include ^{31}P, ^{13}C, ^{1}H and ^{19}F. The most common element used is ^{31}P (energy transfer, ATP hydrolysis, and intracellular pH). An increase in inorganic phosphate (Pi) from ATP hydrolysis during hypoxia leads to a decreasing ATP/Pi ratio. The phosphomonoester (MP)/Pi ratio is a good predictor of renal parenchymal viability. Acute renal failure is characterized by rapid loss of ATP, increased Pi, and decreased pH. In renal allografts, a decrease in MP/Pi is suggestive of rejection.

Obstructive uropathy: Anatomy is well preserved in acute and subacute cases, while in chronic obstruction the corticomedullary interface disappears. A diuretic MRI may be useful in differentiating anatomical obstruction from its functional counterpart.

Congenital anomalies: MRI provides excellent anatomical definition of congenital anomalies including agenesis, duplication, congenital obstruction, and horseshoe or pancake kidney. Ultrasonography, more readily available and less expensive, is the procedure of choice. However, MRI is warranted with inconclusive ultrasonographic studies.

Renal masses: Ultrasonography and CT are the methods of choice. However, MRI is specifically indicated for evaluation of the renal vein and inferior vena cava. With fat saturation techniques, cysts< 1 cm can be identified. This resolution is similar to that of CT. Cysts have sharp borders and thin walls and lack contrast enhancement. A complicated cyst (bleeding or infection) will have similar changes to those described with CT. MRI offers no advantage in the study of polycystic kidney disease. Calcifications are not detected by MRI. Angiomyolipomas are best studied by CT.

Renal cell carcinoma presents with a spectrum of findings. MRI is very helpful in identifying lesions < 2 cm and is preferred over CT. Additional advantages for staging include multiplanar imaging and better vessel visualization. MRI is the method of choice for detecting thrombus and tumor extension into the renal vessels. Gadolimium enhances tumor signals but does not affect blood signals.

Renal functional assessment: Glomerular filtration can be evaluated with injection of contrast and fast breath-hold gradient echo techniques. MRI provides better spatial and multiplanar resolution than isotopic renography and allows visualization of the kidney even in the absence of function.

Pyelonephritis: The collecting system is seen well with T1 imaging because urine has a low signal. Infected urine has a higher T1 signal than normal and can thus be identified. The kidney may appear swollen and lobar areas of high density may be noted, with abscesses identified as low-density images.

Medical renal disease: Loss of the corticomedullary junction is a very sensitive finding indicating significant renal disease; however, it is quite nonspecific. Exceptions to this rule are sickle cell disease and paroxysmal nocturnal hemoglobinuria. In both, the cortex has a very low signal intensity when compared to the medulla, because cortical iron deposition shortens T2. MRI changes are observed in 30% of patients after extracorporeal shock wave lithotripsy. Findings include parenchymal hemorrhage contusions and subcapsular or perinephric hematomas. Bleeding increases the signal, while contusion and edema produce focal or diffuse loss of corticomedullary differentiation. In ATN, the kidney appears normal, but after contrast

the signal intensity in the renal medulla increases because of proximal tubule edema.

Renovascular disease: The oblique course and small size of the renal arteries limit the usefulness of MRI. However, MRA is a promising tool in the evaluation of renovascular disease, particularly in renal allografts.

Renal allograft evaluation: MRI has no advantage over ultrasonography.

Angiography

Renal Arteriography

The most common use of renal angiography is the detection of renovascular disease manifesting itself as hypertension and/or progressive loss of renal function. In cases of renal trauma, angiography is indicated when vessel damage is strongly suspected. Angiography is necessary at times for differentiating avascular benign cystic lesions from neoplasms that are usually highly vascularized. Of note, about 10% of renal cell carcinomas are avascular.

The femoral artery is the preferred entry area; if unavailable, the axillary approach is a reasonable alternative. Before angiography, platelet counts, prothrombin, partial thromboplastin, and bleeding times should be checked and corrected when abnormal. Solid food is restricted from midnight and fluid intake is encouraged, as adequate hydration and fluid expansion can substantially lessen contrast nephrotoxicity. Modern computer technology allows real time recording of images, digital subtraction arteriography (DSA), postprocedure processing for enhancement, less use of film, and lower contrast loads. The major disadvantage of digital techniques is motion artifact. Use of smaller diameter catheters (≤ 5 French) and computer assistance have made angiography a routine outpatient procedure (Table 7). The complication rate of the procedure itself is < 1%, including hematomas, thrombosis, arteriovenous fistulae, pseudonaneurysms, and infections.

A pigtail catheter is placed at the presumed level of the renal arteries (first lumbar vertebral body). A bolus dye injection (≤ 4 mL/kg) is made, and films are taken at a rate of at least 2/sec. After identifying the origin of the renal artery, a curved catheter is positioned and selective renal arteriograms obtained. A single renal artery is found in about 70% of patients. As it reaches the hilum, the main renal artery branches into several segmental vessels, which subsequently divide into interlobar arteries that traverse between the renal pyramids. The interlobar arteries give rise to arcuate arteries that curve around the medulla and run parallel to the cortex. The intralobular arteries branch out at right angles from the interlobar segment. Initial images are taken in the anteroposterior view. Lateral views are then obtained to better evaluate the renal ostia. Upon completion the catheter is removed and compression applied for 10 minutes. The patient usually remains in bed rest for 4 – 6 hours. When appropriate, venous renin samples are obtained from the renal veins and the inferior vena cava.

Renal artery stenosis: The most common cause is atherosclerosis. Most frequent location is the main renal artery and its proximal branches. Plaques may be smooth or irregular and at times accompanied by poststenotic dilatation. Ostial stenosis is usually aortic in origin. Fibromuscular dysplasia is most common in white females younger than 40. There are 4 major types: I. medial fibroplasia with aneurysm formation (70%) presenting as the classic string of beads; II. perimedial fibroplasia (15%) with a string of beads smaller than the unaffected segments of the vessel; III. intimal fibroplasia; IV. periarterial fibroplasia. The latter 2 are associated with

decreased renal mass and small circumferential stenoses. Angiography can also be used for detection of renal allograft arterial stenosis.

A renal vein to inferior vena cava renin ratio ≥ 1.5 with contralateral renin suppression is very specific for renovascular hypertension. However, because of a 50% false negative rate, many centers perform angioplasty without waiting for renal vein renin results. Percutaneous transluminal angioplasty is extensively used for the treatment of renal artery stenosis. Results are best in medial fibroplasia. Atheromatous disease that is short, segmental, and not ostial is reasonably well treated by angioplasty (70 – 90% patency at 12 – 18 months with good blood pressure control in 60 – 70% of patients). Restenosis occurs in 10 – 20% of patients within the first year and is most common in patients with ≥ 30% residual stenosis after angioplasty. Ostium lesions respond poorly to angioplasty and may be best managed by stenting. Complications include ARF (2%), worsening of renal function (2%), and development of arterial rupture, perforation, dissection, segmental occlusion, symptomatic embolization, false aneurysm, fistula formation, or puncture site trauma (10%). Less than 4% of these require surgical correction. It is important to remember that atherosclerotic stenosis may not cause hypertension.

Renal artery aneurysms: These tend to be focal and saccular and are usually located near the hilum. About 30 – 50% have a calcified wall. They are seen in 1% of renal arteriograms and are most commonly associated with stenosis. The risk of rupture is 6%.

Embolic renal disease: May result from left atrial or ventricular thrombus, atrial myxoma, cardiac valvular vegetations, or mural thrombus within an aneurysm in the aorta or renal artery, and may be precipitated by angiography. Cholesterol embolic disease may be identified by pruning of vessels in the appropriate clinical setting.

Vasculitis: The distal vessels are most affected. In periarteritis nodosa, multiple 1 – 3 mm punctate aneurysms may be noted in the distal renal artery branches.

Other vascular lesions: In renal infarction, an occluded vessel may be identified in association with a wedge-shaped radiolucent defect. Arteriovenous fistulae usually result from trauma and are characterized by rapid shunting to the venous system. Arteriovenous malformations have the appearance of serpentine arteries that opacify quite early.

CO_2 Angiography

Currently limited to a few centers but receiving increasing attention for its ability to provide adequate definition of vascular anatomy without use of iodinated contrast agents. Because this technique allows multiple studies without risk of nephrotoxicity, it has great potential for screening patients with suspected occlusive renal arterial disease. Studies comparing CO_2 angiography and flush aortography (without selective catheterization) indicate an 83% sensitivity and a 99% specificity with this technique. Peripheral vessels of the lower extremity are well seen and may provide a particular advantage for evaluation of renal allograft arterial stenosis. The most significant side effect of CO_2 angiography is neurotoxicity (multifocal ischemic infarction due to gas embolization). It is also contraindicated in patients with significant pulmonary disease, as they may be unable to excrete a large CO_2 load. Concomitant congestive heart failure is also of concern because it may be associated with livedo reticularis, rhabdomyolysis, and intestinal infarction from gas embolization following aortography. Lack of commercially available CO_2 injectors and the

need for tilting tables also limit the widespread use of this technique.

Intravenous Digital Subtraction Angiography

It is rarely used at present. On the other hand, dye injection into the right atrium makes DSA suitable for follow-up assessment of percutaneous interventional procedures.

Renal Venography

There are very few indications for venography because it has been replaced by MRI. A renal vein thrombus may be seen angiographically as a radiolucent filling defect or as a venous occlusion.

Transcatheter Embolization

Used in the treatment of neoplasms and arteriovenous fistulae or to control bleeding. Embolization can be done with autologous clot, Gelfoam, polyvinyl alcohol coils, detachable balloons, or absolute alcohol. Many patients develop a postembolectomy syndrome characterized by malaise, fever, local pain, and leukocytosis lasting 3 – 5 days.

Radionuclide Studies

Glomerular Filtration Rate

Available radionuclide agents excreted only by glomerular filtration include iothalamate, diethylenetriamine pentaacetic acid (DTPA) and ethylenediamine tetraacetic acid (EDTA). Most accurate clearance values are obtained using standard clearance techniques (as described previously for inulin) including timed blood and urine samples. ^{125}I-iothalamate (614 dalton) may also be administered as a subcutaneous bolus injection obviating the need for a constant infusion. It provides GFR values identical to those obtained with inulin. Because of the prolonged half life of the isotope (60 days), concomitant Lugol administration is required to protect the thyroid. Values obtained with ^{51}Cr-EDTA (292 dalton) are 10% lower than inulin, perhaps because of in vivo protein binding, tubular reabsorption, or in vivo dissociation. The disadvantage in using ^{99M}Tc-DTPA (393 dalton) is that its short half-life of 6 hours requires preparation immediately before administration and prompt counting of samples. Protein binding also results in lower clearance values when compared to inulin. Radiation is always an issue. Although less than with a standard radiologic procedure, there is transient accumulation in the urinary tract during excretion. It is recommended that patients ingest large amounts of fluid the day of the study. These methods are most commonly used as a replacement for inulin clearance measurements.

Radionuclide agents can be used to assess GFR without collection of timed urine specimens. A single injection or a continuous infusion technique may be used. GFR is measured as the amount of injected radiolabel cleared from plasma divided by the integrated area of its plasma concentration over time curve. Mathematical modeling must be used because it is not possible to obtain enough samples to directly measure the area under the curve. The method presumes that arterial and venous compartments are in prompt equilibrium. Both single and double compartment models have been used. Because the latter requires multiple sampling, the one-compartment model is most commonly used in the clinical setting. Clearance is described by the equation

$C = V_O (\ln (2)/t^{1/2})$

where C = clearance, V_O = initial volume, ln = natural logarithm, and $t^{1/2}$ = radiolabel half-life.

This technique is quite accurate and as few as 2 samples are enough. Second sampling time should be adjusted to the probable level of GFR as follows: 1 hour for near normal function, 4 – 5 hours for moderate renal failure, up to 24 hours for severe chronic renal failure or, regardless of renal function, when significant ascites is present. A shorter single plasma method assumes that the volume of distribution (*Vd*) is given by the dilution of the administered dose (D) at the time of sampling (t). At about 3 hours when the tracer concentration has reached equilibrium, *Vd* can be calculated as D/Pt. Because the radiolabel disappearance rate is proportional to GFR and *Vd*, the former can be mathematically derived. This technique loses accuracy at GFR < 30 mL/min.

In the absence of plasma samples, total GFR can be calculated by gamma camera capture of the activity time curves (renogram) generated over the kidneys. The renogram consists of an initial spike related to the immediate uptake of the arterial bolus (aortorenal transit time), a renal parenchymal transit time segment, and a final pelvic transit time. Absolute estimates of GFR using this approach have a 20% variation and are less accurate than plasma sampling. However, an important advantage of this technique is the ability to measure the relative contribution of each kidney to total function as determined by the individual activity time curves generated. A normal peak occurs at about 150 – 180 seconds. As the first 90 seconds are unstable due to mixing, measurements are made from 90 – 180 seconds. The normal range of relative uptake function is 42.5 – 57.5 %. Estimation of relative renal function is the most important measurement obtained with radionuclide techniques. Results are accurate and reproducible (6% variation). Errors increase when overall GFR is < 20 mL/min.

Renal Plasma Flow

Radiopharmaceuticals, which are primarily secreted by the tubules, provide a reasonable index of renal blood flow. Agents include para-aminohippurate (PAH), orthohippurate (OIH), and mercaptoacetyltriglycine (MAG3), labeled with ^{131}I or ^{99m}Tc. In general, ^{99m}Tc-MAG3 is considered the agent of choice. After injection, samples are taken at defined intervals (7, 17, 30, 44, 60, and 120 min). Calculations using two (7, 17 min) and one (44 min) samples are also available but have a greater coefficient of variation.

Dynamic Diagnostic Imaging

Renovascular hypertension: Stenosis of the renal artery will decrease uptake, increase transit time, and delay tracer excretion on the affected side. The sensitivity of renography in the diagnosis of renovascular hypertension is similar to that of rapid sequence IVP (70% sensitivity and 79% specificity). Diagnostic accuracy is improved by performing renography before and after captopril administration. Captopril induces a further acute decrease in renal blood flow and GFR on the affected side, thereby magnifying the asymmetry of the renogram curves and cortical retention (90 – 95 % sensitivity and specificity). Prior furosemide administration may further enhance differences. Normally, uptake is maximal at 1.5 – 2.5 min, and the difference be-

tween kidneys is no more than 60:40%. Findings suggestive of renal artery stenosis include the following: I. less than 42% accumulation of tracer, II. a delay of >1 min in peak time, and III. increased residual activity at 15 – 20 min. In mild stenosis the latter may be the only positive finding. Lateralizing findings are less likely to be apparent when GFR is significantly decreased.

Vesicoureteral reflux: This abnormality may be assessed directly or indirectly. The direct method is identical to a micturating cystogram but has the disadvantage of offering no anatomical detail. On the other hand, it uses less radiation exposure and is more easily quantifiable. The indirect technique employs a standard dynamic ^{99m}Tc-DTPA renal scan. Upon completion of the test, the patient drinks until the bladder feels full and there is an urge to void. Baseline renal and bladder counts are taken at this point. The patient then voids while the gamma camera updates data for several minutes after voiding. The presence of reflux into the kidney is detected in the time-activity curves as a peak. Lesser degrees of reflux are more prone to error and not easily identified by this method.

Obstructive uropathy: Ultrasonography is the best modality for detecting obstruction (90 – 95% sensitivity and 70% specificity) but provides no functional data. This may be of particular importance in neonates, in patients with previous urological surgery, and in those who have recently passed a kidneys stone. An atonic collecting system appears like hydronephrosis in the absence of obstruction. A furosemide renogram can separate true obstruction from functional dilatation. A standard renogram identifies obstruction as a prolonged transit time. After a standard renogram, a single IV dose of furosemide is given (0.5 mg/kg) and data collected over 15 min. A normal response is a steeping of the rate of fall with a concave washout curve. The absence of washout indicates obstruction. In retroperitoneal fibrosis, ultrasonography may show no hydronephrosis, but the renogram will demonstrate progressive accumulation of tracer without excretion.

Acute renal failure: Isotopic renography is not particularly helpful in the evaluation of patients with ARF. It identifies blood flow to the kidney and the presence or absence of functional tissue. ATN has a normal perfusion phase followed by moderately good visualization at 90 – 180 seconds. Tracer density then gradually decreases with little accumulation in the collecting system. Acute GN and acute interstitial nephritis are characterized by delayed perfusion, very slow accumulation, and virtually no excretion.

Chronic renal failure: Nuclear studies are of very little help. Scans may identify small scarred kidneys or the presence of polycystic kidney disease.

Renal transplantation: The most commonly used agent is ^{99m}Tc-MAG3. Delayed graft function is characterized by good perfusion and decreased function, while in acute allograft rejection both are decreased. Cyclosporine toxicity is indistinguishable from delayed graft function. Isotopic renography may assist in the detection of a suspected urinary leak. In many centers, routine early postoperative isotopic renography is being replaced by color Doppler ultrasonography.

Static renal imaging: Increased gallium uptake is a nonspecific indicator of inflammation. This test will be positive in the presence of acute pyelonephritis, acute interstitial nephritis, and neoplastic infiltration.

Urological Procedures

Major indications for urological interventions encompass abnormal bladder function, suspected lesions (benign or malignant), presumed lower tract bleeding, intra/extraluminal ureteric lesions, the need for precise definition of the collecting system, and evaluation of vesicoureteric reflux. Urological procedures of interest to the nephrologist include cystoscopy, retrograde and antegrade pyelography, cystourethrogaphy, and upper tract endoscopy and lithotripsy.

Retrograde pyelography: Contrast is injected directly into the ureter or ureteral orifice for direct visualization of the collecting system and ureter. The degree of distention and opacification is controlled by the amount of dye and the injection pressure. The ureter can be cannulated cystoscopically and the catheter advanced to the desired level for dye injection (direct), or a bulb-shaped catheter may be wedged to the orifice for injection (bulb pyelogram). If a suspected lesion is found, brush cytology should be performed at the same time. Overdistention may cause pyelosinus extravasation due to fornix rupture and extravasation into the renal sinus, pyelolymphatic extravasation, and/or pyelotubular back flow to the papillary distal collecting ducts.

Renal pelvis tumors are best screened for with retrograde pyelography. Hematuria is the most common clinical presentation, with obstruction noted on occasions. Flank pain, dysuria, or palpable mass are distinctly unusual. Exposure to metabolites of aminophenols is associated with a higher risk. Individuals who consume large amounts of phenacetin are also at greater risk. Renal pelvis tumors account for < 10% of renal tumors. Most common are transitional cell carcinomas, which are twice as frequent in males as females and peak in the 7th decade of life. They may occur anywhere in the urothelium but are 15 times more common in the bladder than in the ureter or pelvis. Lesions may be flat or papillary, with 20% containing metaplastic squamous changes. The papillary types are easier to detect and are usually less malignant. Flat lesions are harder to find, are more malignant, and include squamous cell carcinomas. Multicentric lesions are very common in the bladder and in about 30% of pelvis tumors.

Antegrade pyelography: Contrast is directly injected into the collecting system. It is usually performed when IVP fails and retrograde studies are considered risky or not possible. In children this is the preferred method because cystoscopy is problematic. It is usually done under ultrasonographic or CT guidance.

Cystography: Mainly used for assessment of low-pressure vesicoureteral reflux or bladder rupture. Voiding cystography can be done using a drip method or a direct injection via a urethral catheter. The study may demonstrate low-pressure vesicoureteral reflux, radiolucent filling defects (tumor or radiolucent stone), bladder diverticuli, or vesicocolic fistulae. The bladder is usually filled until the patient feels the urge to void. The catheter is then removed and the patient voids. A cine or video is obtained during voiding and recorded in spot films, 100 mm cut film, or continuous 105 mm film. High-pressure reflux, bladder extravasation, and small neck diverticuli may not be apparent until the voiding study is obtained. For air contrast cystography, the bladder is first coated with barium, drained, and then insufflated with air, CO_2, or nitrous oxide. This technique has better resolution and allows visualization of lesions located within diverticuli or those too small to be detected by standard cystography.

Retrograde urethrography and voiding cystourethrography (VCUG): These are indicated in male patients with neuromuscular bladder dysfunction. A Foley catheter is inserted into the fossa navicularis and the balloon inflated with 1 mL of saline. Contrast is injected via the Foley and the bladder filled. The catheter remains in place during the voiding study. If low pressure reflux is noted, abdominal compression is applied to prevent reflux into the kidneys.

Dynamic retrograde urethrography: This procedure is done using a Foley catheter (preferred method as above) or a Brodny clamp. The latter is a device that has an external meatal plug that is fitted over the glans penis by a traction clamp. The study should be followed by VCUG.

Urodynamic studies: Cystometry measures changes in intravesical pressure with progressive increases in bladder volume. The cystometrogram (CMG) evaluates the filling and/or storage phases of detrusor contraction and consists of four phases:

- I. the initial rise to achieve bladder resting pressure,
- II. the tonus phase where filling causes little change in pressure (400 – 750 mL at < 15 cm H_2O),
- III. the peak capacity at which additional volume causes a rise in pressure while the patient is still able to suppress involuntary voiding, and
- IV. the last phase is voluntary voiding. This evaluation detects bladder compliance abnormalities, involuntary detrusor contraction, and decreased bladder volume.

Uroflowmetry allows the recording of flow volumes and patterns. Flow rate is a function of the combined activity of detrusor and urethra. Urethral obstruction may be overcome by a more forceful detrusor contraction. The normal flow pattern reaches a maximum rate within one third of the total voiding time, with ≥ 45% of the total void volume evacuated within the same period. Mean flow rate should equal 50% of the maximum rate achieved. An interrupted stream is suggestive of striated sphincter contraction, detrusor sphincter dyssynergia, or artifact. Outlet obstruction is characterized by a flat, elongated curve with a low maximum flow rate.

Residual urine volume also gives an index of poor detrusor function and/or bladder outlet obstruction. The larger the volume, the more likely the detrusor hypocontractility. Neurogenic bladder is a term used to describe neuromuscular dysfunction of the detrusor muscle and the urethral sphincter. In this condition, the normal reciprocal parasympathetic and sympathetic activity is inhibited and results in voiding difficulties. Urological evaluation for this condition includes urodynamic studies, electromyography, and radiology. Dual-microtipped pressure transducer catheters allow simultaneous measurement of bladder and urethral pressures. Within the bladder, readings are obtained at the bladder neck, distal sphincter, and bulbous urethra. Sphincter dyssynergy can be easily detected at the internal and distal sphincter sites. Urinary flow measurements are also helpful in evaluating bladder emptying. Normal values for males under age 40 are 22 mL/sec; these drop to 13 mL/sec by age 60. In females normal values for age < 50 are 25 mL/sec and decrease to 18 mL/sec thereafter. Striated muscle activity is assessed by inserting an electromyographic needle into the external sphincter. Normal activity is present at rest, increases with rising intraabdominal pressure, and ceases upon voiding. In upper motor neuron lesions, no increase in electrical activity during rising abdominal pressure is noted because of discontinuity of the neural pathway. Continuous activity during voiding indicates

dyssynergia. An areflexic bladder shows no activity at any time.

Endoscopy of the upper urinary tract: This technique is helpful in evaluating patients with a radiolucent filling defect in the upper urinary tract. Patients with unilateral hematuria identified by cystoscopy require a comprehensive evaluation. If retrograde ureterography and upper tract cytology are negative, a CT study is indicated. If this is negative, an arteriogram is indicated. A negative angiogram is an indication for ureteroscopy.

Instrumentation and endoscopy: Cystourethroscopy allows direct visualization of the anterior and posterior urethra, bladder neck, and bladder. Hematuria is the most common indication. In patients with initial hematuria, bleeding is usually urethral or prostatic. In total hematuria, the source is likely the bladder or the upper tract. Terminal hematuria usually arises from the bladder neck. Next in frequency is the presence of voiding symptoms (obstructive and/or irritative). Visualization of the upper urinary tract can also be accomplished by flexible ureteroscopy. A case of essential hematuria localized to the right or left supravesical collecting system is an indication for ureteroscopy. Anatomical sites of hematuria, when found, can be treated by direct fulguration.

Local bladder pathology commonly identified by cystoscopy includes filling defects, foreign bodies, cystitis (infectious or inflammatory), diverticuli, herniation, tumors (leiomyoma, hamartoma, nephrogenic adenoma, fibrous polyp, papilloma, transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma), and bladder calculi.

Extracorporeal shock wave lithotripsy: Shock waves can be reliably reproduced by the underwater discharge of a capacitor. These waves propagate to the stone without energy loss or tissue damage. They can be precisely focused by integrating the energy source into a suitable reflecting system. Shock waves give rise to mechanical stresses in brittle materials such as kidney stones and cause disintegration. Except for cystine stones, human calculi can be dealt with at low levels of pressure (700 – 900 bar). Side effects include hematuria, perirenal hematoma, parenchymal hemorrhage, edema, tubular necrosis, and fibrosis. The hemorrhage and edema are similar to blunt renal trauma and are short lived.

Renal Biopsy

Examination of renal tissue obtained by biopsy is a crucial component of disease management in clinical nephrology. While correlations between clinical disease and histologic change had long been derived from autopsy material, the introduction of percutaneous biopsy methods dramatically expanded the understanding of glomerular disease in particular.

Current practice incorporates use of a renal biopsy to establish a specific diagnosis when other clinical assessment of renal disease by history, physical examination, urinalysis, and serology is inconclusive. A precise diagnosis has the potential to influence selection of medical therapy. The biopsy may also be helpful in defining prognosis of certain disease states, and in limited circumstances may assess the evolution of renal disease by serial examination of tissue samples over time.

Indications for Renal Biopsy

The most common settings for considering renal biopsy are the evaluation of the neph-

rotic syndrome or nephrotic range proteinuria, acute nephritis, and acute renal failure of obscure origin. Biopsies are also commonly done to evaluate renal dysfunction in transplanted kidneys. Less commonly, a biopsy may be undertaken in the evaluation on non-nephrotic range proteinuria and isolated hematuria. It is important to emphasize that the decision to pursue an invasive diagnostic study such as a biopsy always be individualized, and that the clinical utility of biopsies varies markedly depending on clinical circumstances.

Nephrotic range proteinuria (≥ 3.0 g/24 hours) is classified as secondary if due to systemic disease and primary or idiopathic if an underlying nonrenal disease is not identified. Most clinicians consider a renal biopsy in adult patients with nephrotic proteinuria when diabetes mellitus , amyloidosis, multiple myeloma, hereditary nephropathies, and certain infections have been excluded. The best clinical judgment before biopsy can differ from the biopsy diagnosis in 45% of patients, with modification of planned therapy in 35% of these same patients. Because treatment alternatives for idiopathic nephrotic syndrome remain somewhat limited, other clinicians have advocated use of a decision analysis model advocating use of empiric therapy with corticosteroids. This approach assumes that diagnoses other than the common forms of idiopathic nephrotic syndrome (membranous nephropathy, focal and segmental glomerulosclerosis, minimal change disease, and membranoproliferative glomerulonephritis) occur in only 2% of cases. Some clinicians have found that patients clinically judged to have idiopathic nephrotic syndrome have other diagnoses established by biopsy more frequently. Moreover, treatments with cytotoxic and immunosuppressive agents are currently considered in the treatment idiopathic nephrotic syndrome. It is important to discuss the relative utility of renal biopsy with patients before recommending a renal biopsy for evaluation and treatment of idiopathic nephrotic syndrome. A wide array of issues such as age, co-morbidities, and level of renal function should be addressed.

The renal biopsy may also be useful in evaluating proteinuric conditions in patients with systemic disease. The best example is lupus nephritis. In this setting, even though diagnosis is rarely the issue, the specific morphology of renal involvement guides the choice of therapy. A standardized set of criteria (World Health Organization classification of lupus nephritis) has been developed to assist the clinician in deciding on appropriate treatment regimens. Additionally, an NIH-modified semiquantitative histologic scoring system for lupus nephritis with scales grading the inflammatory activity and chronicity of biopsy lesions has been described and correlated with clinical outcomes.

Investigation by renal biopsy of patients with less than nephrotic range proteinuria (0.5 – 2.5 g/day) is not routinely undertaken in clinical practice. The etiology of such proteinuria is frequently nonspecific. This in no way lessens the importance of a prudent search to explain the proteinuria by other, less invasive clinical methods. On the other hand, biopsies have occasionally been undertaken in such situations and have even led to the description of new forms of uncommon renal disease. Clinical judgment is key in deciding which patients may benefit from this procedure.

Renal biopsy in patients with an acute nephritic syndrome is commonplace. It is particularly useful when abnormal renal function is only of short duration, and clinical evaluation does not identify an immediate specific diagnosis. Patients with rapidly progressing glomerulonephritis (RPGN) are a distinctive subset. In this clinical setting an active urinary

sediment, often with dysmorphic erythrocytes and occasionally red cell casts, is noted in association with variable degrees of proteinuria and hematuria. The differential diagnosis of an acute nephritic syndrome is broad and includes several forms of glomerulonephritis, thrombotic microangiopathies such as hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP), and (rarely) unsuspected hypersensitivity interstitial nephritis or atheroembolization. The importance of distinguishing these processes cannot be overstated, as therapies range from supportive in the case of poststreptococcal glomerulonephritis (PSGN) to immunosuppression with plasmapheresis and cytotoxic drugs in the case of antiglomerular basement antibody-mediated renal disease.

Investigation of ARF by biopsy is generally limited to special clinical situations. In most circumstances, the clinician can reasonably assess the cause of the renal dysfunction without the aid of the biopsy. Prerenal states such as volume contraction and congestive heart failure are usually clinically apparent. Postrenal causes of renal dysfunction are generally best elucidated with imaging techniques, particularly renal ultrasound. Persistent renal failure due to intrarenal processes is most commonly related to acute tubular necrosis due to hypotension or drug toxicity. However, when ARF is associated with a persistent and very active urinary sediment, a biopsy may be invaluable. A renal biopsy may occasionally be utilized in the absence of an active urinary sediment when the clinical cause of prolonged acute renal failure is of obscure etiology. In this situation, common biopsy findings include ATN, interstitial nephritis, atheroembolization, or cortical necrosis. These conditions may require different treatment strategies and have varying degrees of possible recovery of renal function, thereby justifying the use of this invasive procedure. In this setting about 20% of patients will have a change in treatment plan based on the renal biopsy findings.

In the setting of renal transplantation, a biopsy is most commonly undertaken to evaluate renal dysfunction. Acute allograft rejection is often difficult to distinguish from more benign causes of allograft dysfunction, such as nephrotoxicity due to cyclosporine or tacrolimus. Biopsies are also very useful in characterizing the severity and nature of rejection (cellular vs. vascular) and are of help in selecting appropriate antirejection therapy. A standardized classification system, the Banff classification, is very useful in clinical practice and also allows comparisons between patients treated at separate centers. When performing routine biopsies in renal transplant recipients as part of an established protocol, some centers have reported many patients with histologic evidence of rejection in the absence of clinical findings, including renal dysfunction.

The evaluation of hematuria may result in the use of a renal biopsy, although in most circumstances this is not routinely recommended. Patients with hematuria come to the attention of the nephrologist when other investigations, usually including structural studies such as IVP, ultrasound, or CT with contrast agents, and cystoscopy with retrograde studies have not yielded a diagnosis. In this setting microscopic hematuria and/or recurrent macroscopic hematuria may reflect an abnormality of the renal parenchyma. Typically patients with this presentation have normal renal function as assessed by serum creatinine. The principal clinical diagnoses to consider include IgA nephropathy, hereditary nephritis (Alport syndrome), thin glomerular basement membrane syndrome, and the loin pain hematuria syndrome. The prognosis for long-term stable renal function is excellent when there is no concomitant proteinuria. Bi-

opsy is then undertaken primarily to establish a definite etiology of the hematuria and avoid repeated structural imaging studies. However, it should be noted that while frequently abnormal, the renal biopsy is entirely normal in as many as 30% of patients. As more specific treatments are described and validated, such as fish oil in the treatment of IgA nephropathy or angiotensin-converting enzyme (ACE) inhibitors to diminish the frequency of episodes of macroscopic hematuria in thin glomerular basement disease or loin pain hematuria syndrome, the renal biopsy may become more commonplace in patients with isolated recurrent or persistent hematuria.

Specific Considerations Prior to Performance of Renal Biopsy

In counseling an individual patient with one of the above indications for biopsy, the clinician must weigh the likelihood of obtaining information that will change treatment against the risk of the procedure itself. Factors to consider are the presence or absence of coagulopathy, increased renal echogenicity, chronic renal dysfunction, uncontrolled hypertension, a solitary kidney, the inability to comply with verbal instruction, hydronephrosis, active pyelonephritis, or a mass that may be neoplastic. Each of these conditions increases the risk of percutaneous biopsy. The presence of small and echodense kidneys by ultrasound and/or chronic renal dysfunction substantially diminish the diagnostic value of the procedure.

Before percutaneous renal biopsy, patients need to understand that the procedure is a diagnostic study and not a treatment. A platelet count and prothrombin (PT) and partial prothrombin times (PPT) should be obtained. Antiplatelet drugs such as aspirin or other nonsteroidal anti-inflammatory drugs should be omitted for a period of at least one week if the biopsy is elective. Systemic anticoagulants should also be stopped before the procedure. Patients receiving heparin should have the drug discontinued at least 6 hours and preferably 12 hours before the procedure. A PPT should be in the normal range before the biopsy. Warfarin should be stopped long enough for the PT to normalize. In certain high-risk patients who must minimize the period off warfarin, it may be prudent to administer heparin as a short-acting agent after warfarin is stopped and reinstate heparin and warfarin 12 – 24 hours after the biopsy, continuing the heparin until the PT is in a therapeutic range. The use of a bleeding time as a prebiopsy screening study is common but not universally accepted. There are no data indicating that use of this test decreases the risk of hemorrhagic complication after biopsy. Nonetheless, many clinicians continue to use this study. It is probably most relevant in patients with renal dysfunction who may have associated secondary platelet dysfunction. Arginine desmopressin (DDAVP) can be useful in normalizing a prolonged bleeding time in such patients. The clinician should also determine if the patient has 2 functioning kidneys before percutaneous biopsy. An IVP or radionuclide study were previously used for this purpose. A reasonable alternative is an ultrasound evaluation demonstrating 2 kidneys of similar size, and if available, a concomitant Doppler study demonstrating normal perfusion to each kidney.

Biopsy Techniques, Patient Selection, and Tissue Handling

The most widely used biopsy method is the percutaneous renal biopsy. Most clinicians now favor localization of the kidney with

ultrasound techniques because it provides more accurate localization than IVP and obviates the need for radiocontrast material. Additionally it is now possible, and some would argue desirable, to perform the procedure with real time ultrasound monitoring. Smaller bore needles (18-gauge spring-loaded devices instead of 14-gauge needles) are increasingly popular because of the simplicity of their use and the perceived safety of the smaller caliber of the instrument. If there are no anatomic considerations (for example, a large renal cyst at the inferior pole), either kidney may be biopsied, right-handed operators usually sampling the left kidney. The procedure may take place in either a radiology suite or any suitably equipped hospital room. While nephrologists have traditionally performed percutaneous biopsies, radiologists now also frequently perform this procedure.

Sedation is commonplace when children undergo this procedure but is not necessary in adults. After informed consent, the patient is placed in a prone position with a pillow or wedge under the upper abdomen. This has the effect of pushing the kidney toward the back and stabilizing the kidney so that the biopsy needle does not push the kidney away. The inferior pole of the kidney is localized by ultrasound at the time of a held breath in inspiration. The distance from the skin to the capsule of the kidney is noted and a mark is made on the skin where the biopsy needle will enter the skin. The skin is cleansed with an antiseptic solution and the patient is draped to maintain sterile technique throughout the procedure. Local anesthetic, typically 1% lidocaine, is administered superficially to raise a weal in the skin and then carried down to the renal capsule using a 22-gauge needle. A small (0.5 cm) incision is made in the skin to accommodate the biopsy instrument. At this point further localization of the kidney may be undertaken by passing a needle towards the kidney in small increments. When the needle enters the renal parenchyma, a large respiratory excursion of the needle is observed. Additional anesthetic may then be given as the needle is withdrawn. Care is taken to remove the needle in such a fashion as to be able to measure the depth. Some operators now omit this step when the procedure is performed using real time ultrasound guidance. In this circumstance, the biopsy needle may be placed in a guide and the needle brought down under direct visualization to the renal capsule, at which point the biopsy is taken while the patient holds his or her breath in inspiration. In the absence of real time ultrasound guidance, the operator advances the biopsy needle in short increments (0.5 cm) while the patient maintains a held inspiration, and then the operator observes needle swing with respiration. When the needle is anchored in the kidney, the biopsy is performed with the patient maintaining a held inspiration to minimize the risk of renal laceration. Sufficient renal tissue is obtained to submit for the desired studies, including light microscopy and usually immunofluorescence and electron microscopy. A pathologist or technician at the bedside can be helpful in examining the tissue for adequacy with a low power microscope.

After the procedure the patient is placed at bed rest for a minimum of 8 hours, and vital signs are monitored frequently. Serial urines are examined for the presence of macroscopic hematuria. A hemoglobin or hematocrit measurement is sometimes taken several hours after the procedure, although many nephrologists now omit this if obvious clinical complications are not manifested. The patient may be discharged home on the same day, although some physicians still prefer overnight monitoring. Full activity may be resumed 24 – 48 hours after the procedure in most instances. The patient should again be counseled to avoid aspirin or nonsteroidal anti-inflamma-

tory drugs for several days and to immediately report any gross hematuria or unusual flank pain.

In special circumstances, an alternative approach to percutaneous biopsy should be considered. If the need to obtain biopsy material is great and the risk of percutaneous biopsy excessive, the standard alternative is an open procedure using general anesthesia and direct visualization of the biopsied area. This procedure is considered in patients with solitary native kidneys, those with coagulopathies not amenable to complete correction, or those who cannot cooperate by holding respirations. Any factor that might increase the risk of biopsy as listed above is also considered. Several modifications of open procedures have been described and include an approach using local anesthesia through a limited flank incision and a novel transjugular approach in cirrhotic patients with coagulopathies and renal abnormalities. At this time, there are no absolute indications for the use of such alternatives to percutaneous biopsy. For example, it had long been taught that the presence of a solitary native kidney was an absolute contraindication to percutaneous biopsy. A careful analysis of the risks of open biopsy including death related to anesthesia has resulted in a reappraisal of this admonition. Percutaneous renal biopsy has been successfully reported in 9 such patients without serious complication in any and with adequate tissue in 8.

The clinician must also consider other special situations that influence the risk/benefit analysis of a renal biopsy. The role of renal biopsy during pregnancy deserves special mention. Because of the combined risk to the mother and the fetus, most clinicians avoid use of this procedure throughout pregnancy but will undertake the procedure when renal abnormalities persist beyond a reasonable postpartum period. However, biopsies have been performed in women during the first or second trimester of pregnancy for proteinuria with or without hematuria, hypertension, renal insufficiency, and nephrotic syndrome. Adequate tissue was obtained with a percutaneous method in all but 3 cases on initial biopsy attempts. One patient developed hemorrhage 4 days after biopsy while receiving therapy with plasma exchange. Otherwise there were no serious complications. Patients in the ICU receiving mechanical ventilatory assistance with pulmonary-renal syndromes pose a special technical challenge. Seven such patients underwent percutaneous biopsy using ultrasound guidance. Adequate tissue was obtained in all. None had gross hematuria, although 2 patients did receive blood transfusions; however, both had been previously transfusion dependent. Some authors have advocated the use of CT guidance in particularly obese patients in whom ultrasound localization is difficult because of poor resolution of the kidneys. Percutaneous biopsy has been shown to be safe and effective in series of geriatric patients. These patients have a greater likelihood of amyloidosis, membranous nephropathy, vasculitis, and diabetes. Almost one-third of geriatric patients have tubulointerstitial disease as the primary finding. Infants and children can usually be safely subjected to percutaneous renal biopsy if adequate sedation is provided. Real time visualization of the kidney is preferred in these patients. One group has reported on the feasibility of fetal renal biopsy.

Once obtained, the renal tissue must be appropriately handled to yield maximal information. It is imperative that the tissue be treated gently and if the samples are divided, that forceps not be used to avoid crush injury. The sample is placed in a fixative such as Duboscq-Brazil or alcoholic Bouin's solution in preparation for light microscopy. The sample is then transferred into an embedding medium such as paraffin and cut in sections of 1

Table 8. Complications of Renal Biopsy

Complications	Frequency
Major	
Clinically important macroscopic hematuria > 12 hours	0 – 5%
Ureteral obstruction secondary to clot	< 0.5%
Bleeding sufficient to require blood transfusion	0 – 5%
Bleeding sufficient to require surgical exploration	< 1%
Bleeding leading to nephrectomy	0 – 0.3%
Symptomatic perinephric hematoma	0 – 1%
Puncture of viscera (liver, spleen or bowel)	0 – 1%
Sepsis	<0.5%
Death from any cause related to biopsy	0.05 – 0.12%
Minor	
Microscopic hematuria	25% – 100%
Macroscopic hematuria self limited, persisting < 12 hours	0 – 10%
Asymptomatic perinephric hematoma (any size)	
Detectable by CT	Up to 85%
Detectable by routine US	Up to 30%
Traumatic A-V fistula	4 – 18%

to 2 μm in thickness for staining with hematoxylin and eosin, periodic acid Schiff (highlights basement membrane, mesangial matrix, and brush border of proximal tubular epithelial cells), Masson's trichrome (demonstrates areas of fibrosis), Congo Red (a thick section is used to stain for amyloid), and methenamine silver (to search for epimembranous spikes). Samples submitted for immunofluorescence microscopy are promptly snap frozen and then cut on a cryostat at temperatures about –25° C. After a brief period of fixation in acetone, the slides are covered with fluorescein-tagged antiserum in a chamber shielded from light. After several washes to remove unbound antibody, the slides are examined with a fluorescence microscope and photographs taken. Antisera routinely used include anti-IgG, anti-IgA, anti-IgM, anti-C1q, anti-C3, anti-GBM, anti-fibrin, and anti-kappa and anti-lambda light chains. It is also possible in some circumstances to take tissue embedded in paraffin and process it for immunofluorescence microscopy. Samples submitted for electron microscopy are commonly fixed in 3% phosphate buffered glutaraldehyde. The tissue is then post fixed in 1% osmium tetroxide, dehydrated and embedded.

Complications of Renal Biopsy

It is useful to divide complications of percutaneous renal biopsy into major and minor, as detailed in Table 8. Complication rates must be interpreted both in the context of the series size as well as the method of percutaneous biopsy. The largest reported series in the literature did not use real time ultrasound monitoring or smaller (15- or 18-gauge)

spring-loaded needles. More recent series using these approaches report significantly fewer complications.

The most common major complication of renal biopsy is hemorrhage. Gross hematuria is described in most large series as occurring between 2 – 10% of cases. It is generally manifest within the first 12 hours after biopsy but can be delayed up to several days after the procedure in a small minority. In most cases it is self limited. In a series of 127 patients using ultrasound and an automated spring-loaded biopsy needle, 3.1% of patients required transfusions after biopsy. One of these patients required exploratory laparotomy for definitive care. The risk of serious complication was independent of the number of passes to obtain tissue. Patients with poorly controlled hypertension had a higher rate of any complication (7/15 patients; 41 %) compared to 21 complications among the remaining 116 patients (18%). Perinephric hematoma is another serious complication if blood loss is sufficient to cause hypotension or the need for transfusion. Perinephric hematomas are actually quite common if sought by imaging techniques on a routine basis. They are easily detectable by CT in as many as 85% of patients. Clinically significant hematomas with pain, palpable flank mass, or a dropping hemoglobin with or without gross hematuria are far less frequent, occurring in 2 – 6.5% of patients. Perinephric hematoma formation may also be associated with transient renal insufficiency, presumably by compression of renal parenchyma and secondary decrease in blood flow. Inadvertent puncture of intra-abdominal organs such as liver, spleen, and large or small bowel have been reported and may result in serious bleeding, hemoperitoneum, or peritonitis. Fortunately, this is quite infrequent (< 1%) when appropriate measures to localize the kidney are taken. The risk of fatal outcome from any complications due to percutaneous renal biopsy varies between 0.08 – 0.12%. Most modern series do not report any fatalities, but none includes > 1,000 patients in their reports to date.

Lesser complications of renal biopsy not necessitating blood transfusion or an invasive intervention occur in up to 25% of patients. Most exhibit some degree of microscopic hematuria, which most clinicians do not consider a complication. Self-limited gross hematuria not requiring any intervention occurs in 2 – 10% of patients. Traumatic arteriovenous fistulae complicate percutaneous renal biopsies in 4 – 12% of patients and are usually clinically silent and resolve spontaneously. However, they may occasionally be associated with gross hematuria soon after the biopsy and, rarely, high output congestive heart failure, hypertension, or renal insufficiency.

The management of patients with clinically recognized hemorrhagic complications is generally one of close observation. An IV catheter should be placed and blood sent for type and screen if not already done. Frequent monitoring of vital signs is continued. If gross hematuria develops, samples of serial urine voids are saved to assess its resolution. In patients with gross hematuria, the post biopsy observation period should be extended overnight. At a minimum, the patient must remain in the recovery unit until repeated voided urine samples are clear and until stability of hemodynamic parameters and hemoglobin concentration are demonstrated. Normal saline should be administered to maintain a brisk diuresis so as to minimize the risk of clot development in the urinary tract. A urinary bladder catheter need be placed only if patients develop bladder outlet obstruction due to clot retention or if the bleeding is sustained and copious. Bleeding that does not spontaneously resolve requires appropriate use of blood products and further investigation by

CT or ultrasonography looking for a perinephric hematoma or an arteriovenous fistula. Embolization of the bleeding site with selective angiography may be needed. Surgical intervention to control bleeding is the other major alternative. Among all patients undergoing percutaneous renal biopsy, surgical intervention is rare, < 0.3% of cases in modern series.

The observation period after elective renal biopsy is a matter of protocol. Many experienced nephrologists and radiologists monitor patients for 8 – 12 hours post biopsy and then discharge home if no complications are evident. Major complications are usually apparent within 12 hours of the procedure.

Interpretation of the Renal Biopsy

The proper interpretation of the renal biopsy by pathologist and clinician requires that several questions be answered:

- What is the diagnosis?
- How much of the kidney is involved with the pathologic process that is observed in the biopsy sample?
- How reproducible is the biopsy interpretation between different pathologists?
- Can the biopsy material help in defining the prognosis of the patient?

Even one glomerulus can establish a diagnosis of membranous nephropathy or amyloidosis. On the other hand, if a disease state is patchy in its renal distribution, a large sample is required for accuracy. The most common clinical example is making the distinction between minimal change nephropathy and focal segmental glomerulosclerosis (FSGS) in children with nephrotic syndrome. Patients with FSGS may have biopsy findings identical to those of patients with minimal change nephropathy except for a fraction of glomeruli with diagnostic focal sclerosis lesions. If a patient with FSGS has 10% of glomeruli affected with focal lesions and 10 glomeruli are available for examination, there is a 35% chance that the sample will not contain an abnormal glomerulus, leading to an incorrect diagnosis of minimal change disease. If 20 glomeruli are available, there is a 12% chance that a glomerulus with the characteristic changes of FSGS will not be in the biopsy sample. Therefore, the number of glomeruli needed to establish a correct diagnosis is in large measure related to the nature of the diagnosis being considered. Most pathologists view 5 or 6 glomeruli as a minimum for suitable interpretation of a biopsy. When focal lesions are a consideration, 20 glomeruli are a better standard. Similar considerations are applicable when the clinician must decide how truly representative of the whole kidney the biopsy sample is. For example, if a biopsy sample of 10 glomeruli shows 3 with crescents, the likelihood that 30% of all glomeruli have such involvement is only 25%. The chance that the actual involvement is as high as 50% is 1 in 10, and the probability that only 10% of glomeruli are so affected is about 5%. This broad confidence range increases uncertainty in clinical decision making and underlines the difficulties in stratification of patients by biopsy results in clinical trials.

The reproducibility of the pathologist's interpretation has been assessed during evaluation of standardized classification schemes such as the NIH modified semiquantitative histologic scoring system for lupus nephritis and the Banff classification system for interpretation of renal transplant biopsies. In one study 5 pathologists each assessed multiple samples in a blinded fashion; findings were only moderately reproducible. It seems that the more detailed the classification system, the greater the likelihood of inter-and intra-pathologist differences in interpretation.

It is unclear if a renal biopsy can independently predict the patient's renal prognosis any better than other clinical parameters such as creatinine clearance, measured renal size, or degree of proteinuria. It is known that tubulointerstitial damage and fibrosis are more powerful predictors of declining renal function than the percentage of sclerotic glomeruli in a biopsy sample. Some researchers have performed serial renal biopsies to better evaluate renal prognosis. The clinical role of serial biopsies is unclear. However, large amounts of parenchymal damage may be evident independent of observable changes in measured creatinine clearance. Precise quantitative morphometry and assessment of turnover rates of key proteins responsible for renal injury using sensitive polymerase chain reaction (PCR) techniques to evaluate gene activation in biopsy samples may provide new insights of clinical relevance in the not too distant future.

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Hypokalemia, Hyperkalemia, and Metabolic Alkalosis

Kamel S. Kamel and Mitchell L. Halperin

The dyskalemias are common electrolyte disorders that may have serious sequelae, notably cardiac arrhythmias. This chapter will begin with a brief synopsis of the physiology of potassium (K^+), as this information will provide the backbone for our clinical approach to the diagnosis and treatment of patients with hypokalemia or hyperkalemia. The clinical approach to patients with dyskalemias and the tools that can be used to determine "where is the lesion" in the renal handling of K^+ will then be outlined. The approach to therapy of the patient with hypokalemia and hyperkalemia will emphasize circumstances in which these disorders represent a life-threatening condition that requires emergency treatment. Attention will also be given to certain disorders in which new insights into their pathophysiology have been revealed by molecular studies.

Physiology of K^+ Homeostasis

K^+ are the most abundant cations in the body. Close to 98% of K^+ (4000 mmol in a typical adult) exist in the intracellular fluid (ICF) compartment and close to 60 mmol are in the extracellular fluid (ECF) compartment. The ratio of the concentration, $[K^+]$, in the ICF compartment to that in the ECF compartment reflects the resting membrane potential (RMP). The RMP must remain relatively constant in the face of a daily intake of K^+ that is roughly equal to the total content of K^+ in the ECF. Regulation of K^+ homeostasis has 2 important aspects. While the control of the transcellular distribution of K^+ is vital for survival as it acts to limit acute changes in the $[K^+]$ in plasma, it is the long-term regulation of K^+ excretion by the kidney that maintains overall K^+ balance.

Short-term Regulation of K^+ Homeostasis

K^+ are held within cells by an electrical force (inside negative) created by the net exit of positive charges as sodium ions (Na^+) via the Na-K-ATPase and the passive diffusion of K^+ through K^+ ion-specific channels in the plasma membrane.

For K^+ to enter the ICF compartment, the RMP must have a more negative interior voltage. This will occur when Na^+ are pumped out of cells by the Na-K-ATPase, which is an electrogenic ion pump. It exports 3 Na^+ while allowing only 2 K^+ to enter the cell [1]. There-

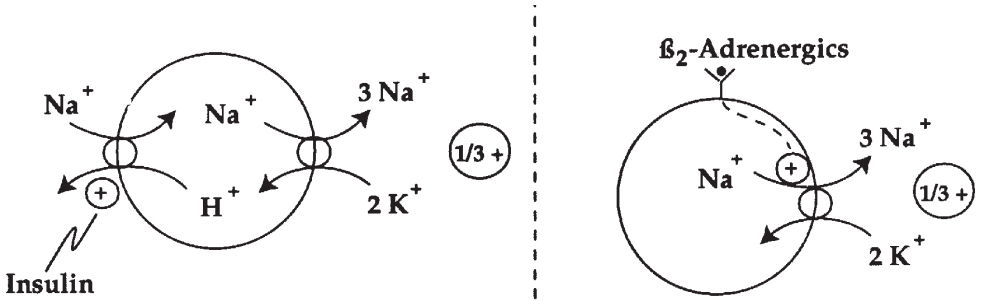

Figure 1. Hormones causing K^+ to shift into cells. For details, see text. The major hormones involved are insulin and β_2-adrenergics.

fore, there is the net export of one-third of a positive charge per Na^+ ion transported (Figure 1). Furthermore, most of the K^+ that enters cells will exit by diffusion through K^+ ion channels in the cell membrane [2, 3]. For every K^+ that exit cells via K^+ channels, there is the net export of one positive charge, creating the majority of the RMP. Some K^+ channels in cell membranes are regulated by voltage, others by calcium (Ca^{2+}), and yet others by adenosine triphosphate (ATP) [2, 3]. Aside from rare conditions such as barium poisoning, specific causes of dyskalemia related to changes in K^+ channel activity are very uncommon.

To increase the absolute magnitude of the RMP and allow more K^+ to shift into cells, there must be a net export of positive charges out of these cells. This occurs only when the Na^+ exported by the electrogenic Na-K-ATPase are Na^+ that already existed inside cells or are Na^+ that entered the cells in an electroneutral fashion, e.g., in exchange for H^+ via the Na^+/H^+ exchanger (NHE-1) [4] (Figure 1). These considerations provide the background for understanding the mechanism of action of the 2 major hormones that affect the transcellular distribution of K^+.

Hormones

– *Catecholamines cause the export of intracellular Na^+*. The effect of β_2 agonists to lower the plasma [K^+] by shifting K^+ into cells is probably the result of stimulation of the Na-K-ATPase via a cyclic AMP-dependent mechanism (Figure 1), which leads to the export of pre-existing intracellular Na^+ [5]. Clinically, hypokalemia due to an acute shift of K^+ may be seen in conditions associated with a surge of catecholamines (e.g. a patient with a subarachnoid hemorrhage, myocardial ischemia, or an extreme degree of anxiety) [6]. β_2 agonists have been used to cause a shift of K^+ into cells in the treatment of patients with hyperkalemia [7].

– *Insulin leads to the electroneutral entry of Na^+*. The effect of insulin to shift K^+ into cells is through its action to promote the electroneutral entry of Na^+ into cells via NHE-1 [4, 8, 9] (Figure 1). This increased entry of Na^+ into cells then stimulates the electrogenic Na-K-ATPase. For this reason, insulin is given to enhance a shift of K^+ into cells in the treatment of patients with severe hyperkalemia by rendering the RMP more electronegative.

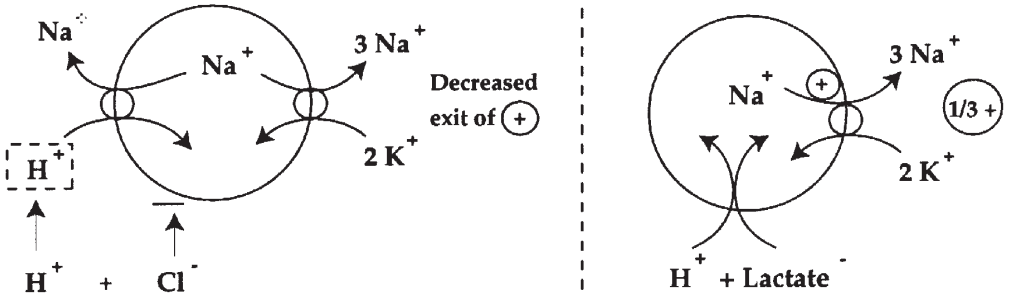

Figure 2. Buffering of H^+ and the consequent K^+ shift. The circles represent the cell membrane. In the left-hand figure, because the acid added is HCl, H^+ enter cells by the NHE-1 and Cl^- remain largely in the ECF. Hence there is a loss of Na^+ from the ICF in this setting. As a result, there is less Na^+ to pump out by the Na^+-K^+- ATPase and the RMP becomes less electronegative. Therefore there is a tendency for K^+ to enter the ECF compartment. In contrast, in the right-hand figure, the acid added is lactic acid, so H^+ enter cells on a cotransporter with lactate anions. As a result, there is no change in the amount of Na^+ to pump out by the Na^+-K^+-ATPase and the RMP does not change. Therefore, there is no tendency for K^+ to enter the ECF compartment.

Acid-base Disorders

When an acid is added to the body, most of the H^+ are buffered in the ICF compartment [10]. A shift of K^+ out of cells may occur if the anions that accompany these H^+ are distributed primarily in the ECF compartment. This is seen experimentally with the infusion of hydrochloric acid in dogs [10]. The extracellular H^+ exchange for intracellular Na^+ via NHE-1 results in less Na^+ in the ICF to be exported by the electrogenic Na-K-ATPase (Figure 2). In contrast, when H^+ enter the ICF compartment accompanied by their conjugate base, there will be no shift of K^+ out of cells (no modification of the electrogenic exit of Na^+). For example, the infusion of L-lactic acid or ketoacids into nephrectomized dogs did not cause a shift of K^+ out of cells because the accompanying organic anions entered the ICF along with their H^+ [11, 12].

Several clinical implications follow from these observations. First, if hyperkalemia is present in a patient with an organic acidosis, a cause for the hyperkalemia other than the acidosis should be sought, e.g. lack of insulin in patients with diabetic ketoacidosis (DKA), tissue injury, or a decrease in the RMP in patients with lactic acidosis [13]. Second, although inorganic acidosis causes the shift of K^+ from the ICF, patients with chronic hyperchloremic metabolic acidosis, e.g. patients with diarrhea or renal tubular acidosis (RTA), usually have a normal or even low plasma [K^+] because of the loss of K^+ in the diarrheal fluid or the urine (reviewed in reference [14]). Therefore, a defect in K^+ excretion is to be suspected if hyperkalemia persists in these patients.

Two other points are worth mentioning. First, although hypokalemia is a common finding in patients with metabolic alkalosis [15 – 17], this reflects renal K^+ wasting for the most part due to the underlying disorder (e.g. vomiting, diuretic use, hyperaldosteronism) rather than the small effect of alkalemia to shift K^+ into cells when H^+ exit. Second, respiratory acid-base disorders cause only small changes in the plasma [K^+], as there is little movement of Na^+ across cell membranes in these disorders [18, 19].

Tissue Anabolism/Catabolism

Intracellular anions do not cross cell membranes for the most part because they are large molecular organic phosphates. Thus, they help retain K^+ in cells.

When anabolism occurs, K^+ along with macromolecular organic phosphates redistribute into cells. Nevertheless, the $[K^+]$ does not rise appreciably in the ICF compartment because the ICF volume also increases (more osmoles but the same osmolality) [20]. Accordingly hypokalemia may be seen in conditions associated with rapid cell growth with the accumulation of intracellular organic phosphates if not enough K^+ is given. Examples include patients with a catabolic state who are treated with total parenteral nutrition (TPN), patients with rapidly growing leukemias and lymphomas, and during the course of treatment in patients with DKA or pernicious anemia. On the other hand, catabolic states are associated with a loss of K^+ and phosphate anions from the ICF compartment. For example, severe hyperkalemia may be seen in patients with crush injury or tumorlysis syndrome [21]. In these patients, factors that compromise the kidney's ability to excrete K^+ are usually present as well. In patients with DKA, tissue catabolism with the loss of organic phosphates from the ICF compartment leads to a parallel loss of K^+ and total body K^+ depletion [22]. There is a large loss of K^+ in the urine because of the high urine flow rate (osmotic diuresis) and high levels of aldosterone (low ECF volume) [23]. These patients usually present with hyperkalemia because there is a shift of K^+ from the ICF compartment to the ECF compartment owing to the lack of insulin [4]. The corollary is that complete replacement of the K^+ deficit in these patients must await the provision of cellular constituents (e.g. phosphates, amino acids, Mg^{2+}),and the presence of anabolic signals.

Long-Term Regulation of K^+ Homeostasis

The rate of urinary excretion of K^+ is a function of 2 factors, the urine flow rate and the $[K^+]$ in the urine. Each must be analyzed independently.

$$K^+ \text{ excretion} = \text{Urine volume} \times [K^+]_{urine} \quad (1)$$

The major site of regulation of K^+ excretion is the cortical collecting duct (CCD) [23]. One must analyze the 2 factors in equation 1 in terms of events in the CCD to understand how the excretion of K^+ might have been altered.

Flow rate in the CCD

The CCD flow rate is directly proportional to the rate of osmole excretion when arginine vasopressin (ADH) acts (ADH acts throughout most of the 24-hour cycle).

$$\text{Flow rate}_{CCD} = (U_{osm} \times \text{Urine flow rate})/P_{osm} \quad (2)$$

where U_{osm} and P_{osm} represent the osmolality of the urine and plasma, respectively. When ADH acts, the major determinant of the CCD flow rate is the number of osmoles to be excreted (equation 2) [24]. Because ADH acts throughout most of the 24-hour cycle [24], a minimum estimate of the flow rate in terminal CCD is obtained by dividing the rate of excretion of osmoles by the osmolality at the end of the CCD (P_{osm} when ADH acts, Figure 3). The major osmole in the urine is urea. Na^+ and chloride (Cl^-) are the other quantitatively important osmoles in the urine. This information is useful clinically. For example, a low rate of osmole excretion can lead to an even lower rate of K^+ excretion and can worsen the degree of hyperkalemia in some patients [25]. Con-

versely, increasing the rate of Na^+ and Cl^- excretion with a loop diuretic can help augment K^+ excretion by enhancing the flow rate in the CCD [26].

$[K^+]$ in the CCD Lumen

Net K^+ secretion is augmented by an electrical driving force (lumen-negative) created by reabsorbing Na^+ faster than Cl^- – the electrogenic reabsorption of Na^+ in the CCD.

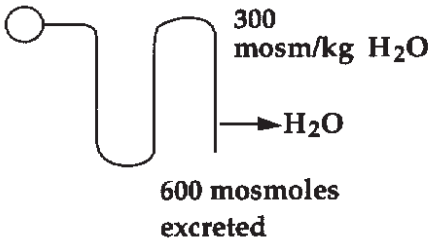

Figure 3. Non-invasive estimate of the flow rate in the CCD. The stylized structure is a nephron. When ADH acts, the osmolality in the plasma and the luminal fluid of the CCD are equal (represented as 300 mosm/kg H_2O for easy math). If 600 mosm are excreted in a given time, the flow rate to the CCD is 2 L under these conditions.

For K^+ secretion, one must also have K^+ channels in an open-configuration in the luminal membrane of the CCD.

Long-term K^+ homeostasis is primarily due to regulation of K^+ secretion by principal cells in the late distal convoluted tubule and the CCD [23]. The generation of a lumen-negative voltage in the CCD requires that Na^+ be reabsorbed at a faster rate than the accompanying anion, usually Cl^-, i.e. electrogenic reabsorption of Na^+ (Figure 4). K^+ channels in the lumen of the CCD are abundant and have a high open probability [2, 3] so they might not be rate-limiting for net secretion of K^+ in most instances.

Sodium: Reabsorption of Na^+ occurs via its specific epithelial Na^+ channel (ENaC) in the apical membrane of principal cells (Figure 5) [27]. Under most circumstances, variations in the luminal $[Na^+]$ in the CCD do not play a role in the regulation of K^+ secretion [28]. Aldosterone causes this ENaC to be in a more open configuration and also increases the number of these channels in the luminal membrane [27]. The steps involved in this action of aldosterone include entry of the hormone across the basolateral membrane and its bind-

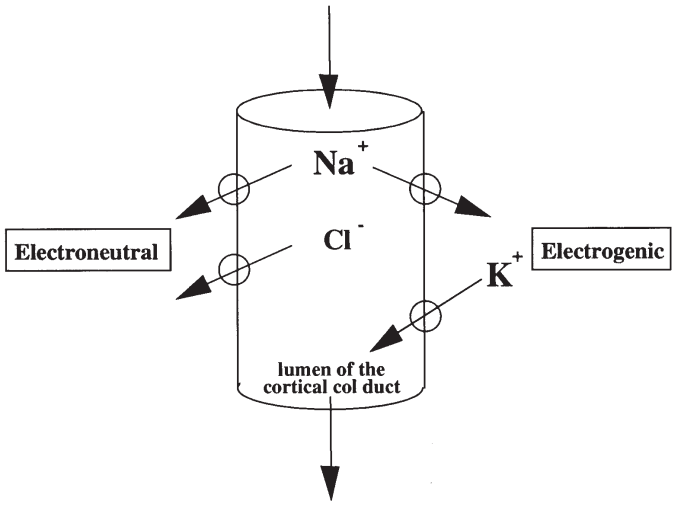

Figure 4. "Electrogenic" and "electroneutral" reabsorption of Na^+. The barrel-shaped structure is the CCD. When Na^+ and Cl^- are reabsorbed in equimolar amounts, there is no transepithelial potential difference (TEPD) created to favor net secretion of K^+; this is termed electroneutral on the left side. In contrast, as depicted on the right side of the figure, reabsorption of Na^+ without Cl^- is electrogenic and generates a TEPD (lumen negative) which drives the net secretion of K^+.

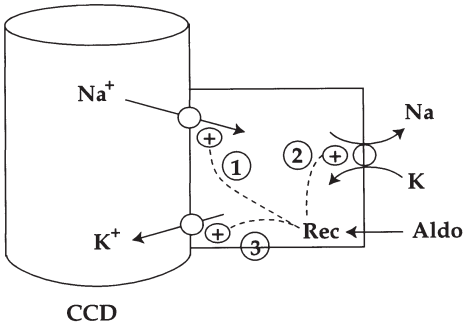

Figure 5. Mechanism of action of aldosterone in the CCD. The barrel-shaped structure is the lumen of the CCD and the rectangle on its right border is a principal cell. Aldosterone (Aldo) enters these cells through their basolateral membrane, binds with its cytoplasmic receptor (Rec), and the hormone-receptor complex enters the nucleus to drive the synthesis of new proteins. In the early phase, this leads to activation of the ENaC (point 1); late phase changes include the synthesis of Na^+-K^+- ATPase pump units (point 2), and luminal K^+ ion channels (point 3).

ing to a cytoplasmic receptor in principal cells. This is followed by entry of this hormone-receptor complex into the nucleus, which leads to the synthesis of new proteins (Figure 5).

Even though the concentration of glucocorticoids is much higher than aldosterone in blood and both have an equal affinity for the mineralocorticoid receptor, glucocorticoids do not usually stimulate K^+ secretion in the CCD. The reason for this lack of effect of glucocorticoids is that principal cells have a pair of enzymes called 11 β-hydroxysteroid dehydrogenase (11 β-HSDH) that converts cortisol to an inactive metabolite (cortisone) that does not bind the mineralocorticoid receptor (Figure 6) [29]. This pair of enzymes acts in concert. First, a low-affinity, high-capacity enzyme destroys most of the cortisol. Second, a high-affinity, low-capacity enzyme removes the remaining cortisol so that there is now an insufficient amount of this hormone

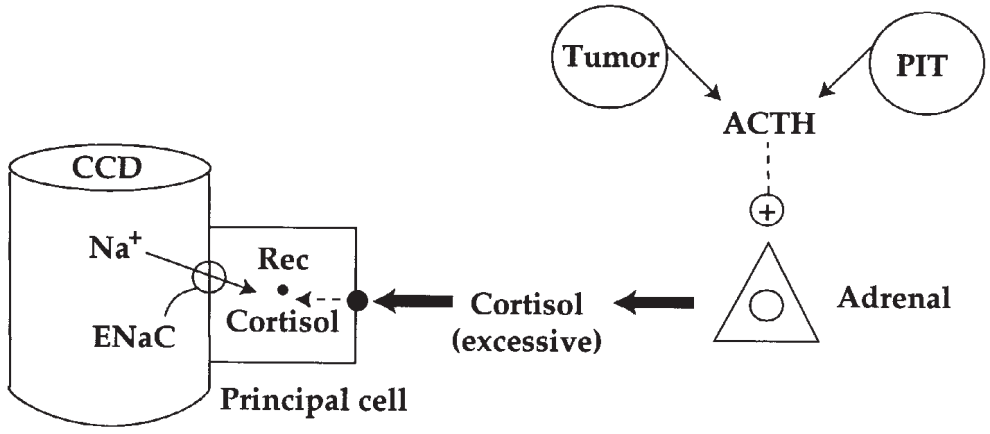

Figure 6. Influence of 11β-hydroxysteroid dehydrogenase on "aldosterone-like" actions in the CCD. Cortisol has a very high affinity to the aldosterone receptor. As cortisol enters principal cells of the CCD, the pair of enzymes 11β-HSDH (shown by the larger solid dot in the membrane), inactivates it before it can bind to the aldosterone receptor (rec, the smaller dot in the cell). There are 3 circumstances in which cortisol will successfully bind to the aldosterone receptor: when there is a deficiency of 11β-HSDH (apparent mineralocorticoid excess syndrome), when an inhibitor 11β-HSDH is present (e.g. licorice), and possibly when there is an excess supply of cortisol relative to the normal activity of 11β-HSDH (perhaps ectopic production of ACTH by a tumor). Abbreviation: PIT = Pituitary gland.

in these cells to bind to the mineralocorticoid receptor. Glucocorticoids, however, can exert a mineralocorticoid effect if the activity of this enzyme is

- decreased, e.g. patients with apparent mineralocorticoid excess syndrome (AME);
- inhibited, e.g. by licorice, carbenoxolone, or a product from swallowed chewing tobacco; or
- overwhelmed by an extreme abundance of cortisol, e.g. patients with ACTH-producing tumors or severe Cushing syndrome (Figure 6).

The K^+-sparing diuretic amiloride [30] and the antibiotic trimethoprim in its cationic form [31, 32] block the ENaC and thereby decrease net secretion of K^+ in the CCD.

Chloride: The pathway(s) for the reabsorption of Cl^- in the CCD is (are) not well defined [33]. Nevertheless, changes in the apparent permeability for Cl^- in the CCD have been postulated to be responsible for the abnormal rate of K^+ excretion in some patients with dyskalemia [34]. For example, a relative increase in Cl^- reabsorption in the CCD is thought to diminish the electrogenic, lumen-negative, driving force for K^+ secretion (the so-called Cl^- shunt disorder). As a result, the rate of K^+ excretion is low, and this could explain the hyperkalemia in patients with Gordon's syndrome [35] and in patients treated with cyclosporin [36] (Figure 7).

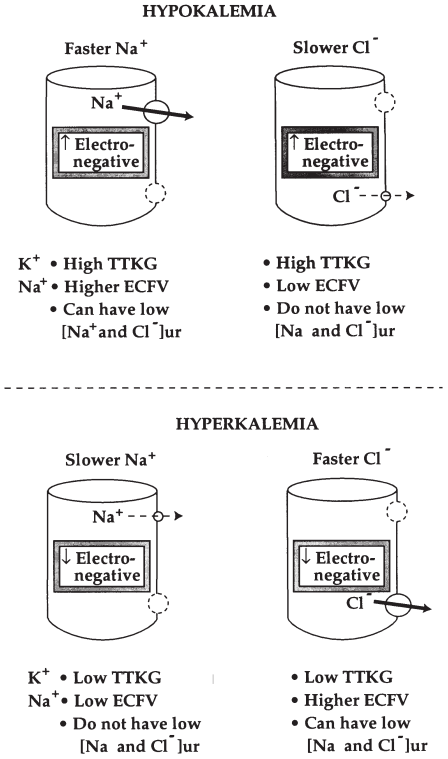

Figure 7. Components of K^+ excretion in the CCD. The barrel-shaped structures represent the CCD. The normal pathway for Na^+ and Cl^- reabsorption are shown in the hatched circles in the luminal membrane. Slower pathways are indicated by smaller open circles with dashed lines and faster ones by larger open circles with bold arrows. Reproduced with permission [104].

Regulation of the apparent permeability for Cl^- in the CCD is important in determining whether aldosterone will be an NaCl-retaining or a K^+-excreting hormone when the ENaC is open (Figure 4) [37]. The presence of bicarbonate ions (HCO_3^-) in the lumen of the CCD seems to be important in this regard. HCO_3^- and/or an alkaline pH in luminal fluid seems to augment net secretion of K^+ in the CCD even when luminal [Cl^-] is high, possibly by decreasing the apparent permeability for Cl^- in the CCD [34]. Thus, aldosterone is allowed to exert its kaliuretic action. On the other hand, a diminished delivery of HCO_3^- to the CCD allows aldosterone to function as an NaCl-retaining rather than as a kaliuretic hormone [37].

Two other points are worthy of mention. First, anions like sulfate that are not reabsorbed in the CCD augment K^+ secretion only in the presence of a very low luminal [Cl^-]. Second, in states where there is a magnesium (Mg^{2+}) deficit, the net K^+ secretion is often

Table 1. Urine electrolytes in the differential diagnosis of hypokalemia. Reproduced with permission [104].

Condition	Urine Electrolyte Na^+	Urine Electrolyte Cl^-
– Vomiting		
Recent	High*	Low**
Remote	Low	Low
– Diuretics		
Recent	High	High
Remote	Low	Low
– Diarrhea or laxative abuse	Low	High
– Bartter's or Gitelman's syndrome	High	High

Values not valid for polyuric states.
*High = urine concentration > 15 mM,
**Low = urine concentration < 15 mM.

augmented, but the mechanisms responsible for this effect are not clear [38].

Clinical implications: To evaluate why the $[K^+]$ is not the expected one for a given abnormality in plasma $[K^+]$, one should try to determine the basis of this abnormality at the ion channel level. In this analysis, one attempts to derive information about the relative rates of reabsorption of Na^+ and Cl^- in the CCD. For example, in a patient with hypokalemia, a higher-than-expected $[K^+]$ in the lumen of the CCD implies that an unusually high lumen-negative voltage is present. This voltage is the result of a relatively faster reabsorption of Na^+ and/or relatively slower reabsorption of Cl^- in the CCD. The converse is true for hyperkalemia. Further analysis requires an assessment of the ECF volume and the expected urine $[Na^+]$ and $[Cl^-]$ when the ECF volume is contracted (Table 1) [26]. Determining this underlying pathophysiology has implications for therapy.

Reabsorption of K^+ in the Distal Nephron

Stimulation of the K^+ reabsorption is usually important when its excretion rate should be low. The transport system involved (H-K-ATPase) can only reabsorb a small quantity of K^+ because an acceptor for H^+ in the lumen is needed.

Reabsorption of K^+ may occur by α-intercalated cells in the CCD and medullary collecting duct (MCD) via a H-K-ATPase [39]. For the H-K-ATPase to operate, there must be luminal acceptors for H^+. Since there is usually little NH_3 and HPO_4^{2-} available in the lumen of the MCD [40], this transport system can only reabsorb a small quantity of K^+.

Clinical Approach to Assessing a Patient with Hypokalemia or Hyperkalemia

Emergency Therapy for the Dyskalemia

Because hypokalemia and hyperkalemia can be life threatening, one should recognize those situations in which a dyskalemia represents an emergency, as priority should be given to therapy rather than diagnosis at this point.

The major danger is a cardiac arrhythmia. This is more likely to occur with acute and/or large changes in the plasma $[K^+]$, especially if there is underlying cardiac pathology or the use of digitalis in a patient who has hypokalemia. Other situations that may represent an

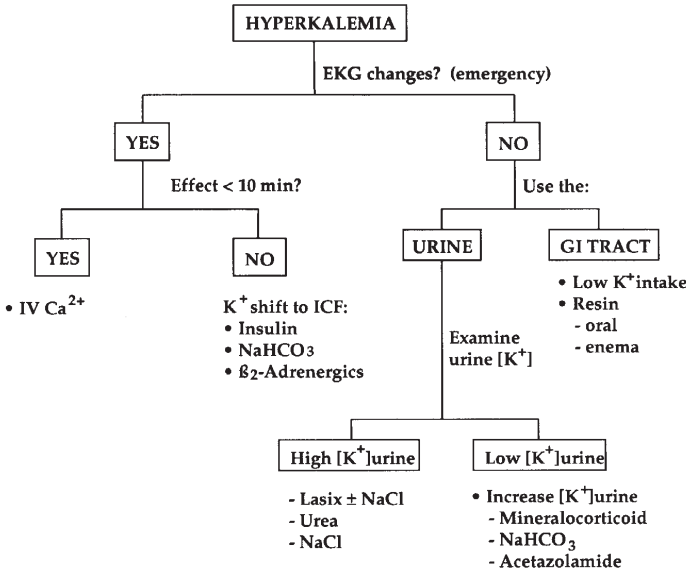

Figure 8. Treatment of the patient with hyperkalemia. If an emergency is present (usually cardiac), IV Ca^{2+} must be given. This treatment should act promptly. Once the emergency is dealt with, or if there is just a severe degree of hyperkalemia, efforts are now to shift K^+ into cells with insulin ± $NaHCO_3$. Longer term strategies are to limit intake of K^+, prevent its absorption in the GI tract, and promote its excretion. In this latter context, examine the urine $[K^+]$ and flow rate to decide leverage for therapy. Reproduced with permission [104].

emergency are if hypokalemia causes respiratory muscle weakness in a patient with respiratory or metabolic acidosis, and hypokalemia in a patient with hepatic encephalopathy.

– *Emergency therapy for hypokalemia*: Enough K^+ should be given to eliminate the cardiac arrhythmia. Replacement of the remainder of the K^+ deficit should be done later and at a much slower pace. If a large dose and hence a high $[K^+]$ need to be given initially, this K^+ should be administered via a large central vein [41]. Electrocardiographic (ECG) monitoring is mandatory. The following example illustrates how much K^+ to give. With a patient who has a severe degree of hypokalemia (plasma $[K^+]$ of 1.5 mM) that led to ventricular tachycardia, the aim of therapy is to raise the plasma $[K^+]$ by 2 mM in 1 min. A typical adult has a blood volume of 5 L, and if the hematocrit is 40% the plasma volume is 3 L. Assuming a cardiac output of 5 L/min, then 6 mmol of K^+ needs to be given in 1 min to achieve the goal. Note, however, that the rise in plasma $[K^+]$ in venous blood will be much < 2 mM because the infused K^+ will be distributed in the larger interstitial volume. Of greater importance, $[K^+]$ will not be high in the interstitial fluid bathing cardiac myocytes with this initial therapy. If the arrhythmia persists, the procedure should be repeated. After this initial bolus, K^+ should be infused at 1 mmol/min, and the plasma $[K^+]$ should be measured in 5 min. With such a high rate of K^+ infusion, vigilant monitoring of the ECG and the plasma $[K^+]$ is an absolute requirement. Administration of glucose or HCO_{3-} should be avoided because either might lead to the shift of K^+ into cells and thus aggravate an already severe degree of hypokalemia.

– *Emergency therapy for hyperkalemia*: Because mild ECG changes may progress rapidly to a dangerous arrhythmia, any patient with an ECG abnormality related to hyperkalemia other than simply peaked T waves should be considered as a potential medical emergency. Patients with a severe degree of hyperkale-

mia (> 6.5 mM) should also be treated aggressively, even in the absence of ECG changes (Figure 8). A note of caution, however, is needed. A severe degree of hyperkalemia is well tolerated in certain settings such as extremes in exercise (the super-marathon [42]) and in infants, so not all hyperkalemia requires the measures described below.

The first step in therapy is to antagonize the cardiac toxicity of hyperkalemia. Ca^{2+} is the best agent, and its effects should be evident within minutes. It is usually given as 10 mL of a 10% calcium gluconate solution. This dose can be repeated in 5 min if ECG changes persist. The effect may last 30 – 60 min. Extreme caution should be exerted using Ca^{2+} in patients treated with digitalis because hypercalcemia may precipitate digitalis toxicity.

The next step is to induce a shift of K^+ into the ICF. The effect of insulin to shift K^+ into cells is rapid [43]. Approximately a 0.6 – 1.0 mM fall in the plasma [K^+] is expected within 30 min, usually lasting for 1 – 2 hours. Usually 6 – 10 units of regular insulin are given. Glucose (50 g) is also given to avoid hypoglycemia, but careful monitoring of the blood sugar is required. Obviously, glucose should not be given if the patient is hyperglycemic.

A second strategy to shift K^+ into cells is to infuse $NaHCO_3$. Recent studies have questioned the efficacy of $NaHCO_3$ to lower the plasma [K^+] in patients with end-stage renal disease (ESRD) on dialysis [44]. Notwithstanding, these patients had only a mild degree of acidosis. The K^+-lowering effect of $NaHCO_3$ may be more prominent in patients with a more severe degree of acidosis. Some studies showed that when combined with glucose/insulin therapy, $NaHCO_3$ did cause a further fall in [K^+] [45]. Excessive administration of $NaHCO_3$ should be avoided because hypernatremia, ECF volume expansion, CO_2 retention, and a fall in ionized Ca^{2+} may occur. In a severely hyperkalemic, acidemic patient with heart failure, phlebotomy may be needed to permit use of $NaHCO_3$.

A third strategy to shift K^+ into cells is to administer β_2-adrenergic agonists. Albuterol or salbutamol (10 –20 mg in 4 mL of saline by nasal inhalation over 10 min or 0.5 mg intravenously (IV)) may lower the plasma [K^+] by 0.6 – 1.5 mM. The peak effect is usually seen within 30 min when these drugs are given intravenously, but it may be delayed for up to 90 min when the nebulized form is used [43, 46]. A significant number of patients with ESRD did not respond to these agents with the expected fall in [K^+]. In a number of studies only a modest increase in heart rate was observed when these drugs were used; however, there is still the potential risk of tachyarrhythmias and myocardial ischemia in patients with coronary artery disease. Considering the inconsistent K^+-lowering effect and the potential for side effects in a population with a high prevalence of heart disease, we do not recommend the routine use of these agents.

In some patients, the rapid removal of K^+ from the body by dialysis may be required. Hemodialysis (HD) is more effective than peritoneal dialysis (PD) for removing K^+. Removal rates of K^+ can be close to 35 mmol/hour with a dialysate bath [K^+] of 1 – 2 mM. A glucose-free dialysate is preferable to avoid the glucose-induced release of insulin and the subsequent shift of K^+ into cells, which limits the removal of K^+. For the same reason, one should also consider discontinuing the insulin/glucose infusion once HD is initiated.

Ensure that there is no Laboratory or Technical Problem

Pseudohyperkalemia may occur because of prolonged fist clenching during blood sampling [47]. Muscular contraction leads to depolarization of cell membranes and the release of K^+ from cells. The local architecture in muscle is important because most K^+ is released locally into T-tubules that minimize their escape into the circulation. If this architecture is disturbed (e.g. in patients who are cachectic), more K^+ is released into venous blood during blood sampling.

K^+ may be released from lysed red blood cells (RBC), but hemolysis is readily detected. K^+ may be released from platelets that have lysed during coagulation, or if they are in contact with glass. For this to cause a significant degree of hyperkalemia, platelets must have a large cytoplasmic volume (megakaryocytes) [48]. In rare circumstances, K^+ may be released from "fragile" white blood cells (WBC) in a patient with leukemia during blood sampling.

Assess the Role of the Kidney as a Cause of the Dyskalemia.

Rate of Excretion of K^+

There is no normal rate of K^+ excretion. In normal subjects K^+ excretion reflects K^+ intake [49]. To assess the renal response to a disorder of K^+ homeostasis, we use the expected rate of K^+ excretion when hypokalemia or hyperkalemia is due to nonrenal causes (Table 2). In subjects who were rendered hypokalemic with dietary K^+ deprivation, K^+ excretion fell to 10 – 15 mmol/day [50]. On the other hand, with chronic K^+ loading, the rate of K^+ excretion can exceed 200 mmol/day [51]. If these expected responses are not observed in patients with hypokalemia or hyperkalemia, respectively, then a renal component to the pathophysiology of their disorder must be present.

Components of K^+ Excretion

Inappropriate flow rate in the CCD: On its own, this will not be a significant problem to cause a dyskalemia (unless it is unduly low, thereby limiting K^+ excretion); nevertheless, it may be a contributing factor. Simply counting the osmoles excreted in a given time period permits this aspect to be assessed (Figure 3) [24].

Inappropriate [K^+] in the CCD: We use the following noninvasive test to help with the assessment of the net secretion of K^+ in the CCD.

– *The transtubular [K^+] gradient (TTKG):* In the first step to calculate the TTKG, the aim is to obtain a reasonable approximation of the [K^+] in the lumen of the terminal CCD [52]. This is done by correcting the [K^+] in the urine for the amount of water reabsorbed in the MCD (Figure 9). To correct for water reabsorption in the MCD, the [K^+] in the urine is divided by the ratio of urine osmolality to plasma osmolality ($(U/P)_{osm}$) because the latter is the same as the osmolality in the terminal CCD when ADH acts. For this calculation to be valid, the osmolality of the urine must be equal to or greater than that of plasma because one must deduce the osmolality of the fluid entering the MCD. In the second step of TTKG calculation, the [K^+] in the terminal CCD is divided by the plasma [K^+] to obtain a semiquantitative index of the driving force to raise the [K^+] in the terminal CCD (equation 3).

$$TTKG = [K^+]_{urine}/[K^+]_{plasma}/(Uosm/Posm) \quad (3)$$

Table 2. Tests to examine K^+ excretion in patients with hypokalemia or hyperkalemia. Reproduced with permission [104]

Test	Advantages	Disadvantages	Expected values
24-hour K^+ excretion rate or K^+ : creatinine ratio	– Indicates overall renal response in patients with hypokalemia or hyperkalemia	– Does not indicate the mechanism responsible for the defect. – Takes 24 h or measurement of creatinine in urine. – Collections are not always accurate.	– Normal: 60 – 80 mmol/day or 6 – 8 mmol/mmol creatinine. – Hypokalemia: < 10 mmol/day or 1 – 1.5 mmol/mmol creatinine. – Hyperkalemia: > 150 mmol/day or 10 – 15 mmol/mmol creatinine.
Fractional excretion of K^+		– Results must be compared with GFR, so it is impractical, and the GFR must be measured.	– Cannot express a normal value without knowing the GFR.
Spot urine [K^+]	Convenience	– Influenced by 2 independent factors: K^+ secretion and water reabsorption in the medulla; thus a wide gray zone	– Hypokalemia: < 20 mmol/day if due to a non-renal cause and > 20 mmol/day if due to a renal cause. – Hyperkalemia: no expected value reported.
TTKG	– Physiological relevance – Separation of $[K]_{CCD}$ and flow rate – Little overlap	Indirect test Must have Uosm > Posm Reabsorption of solutes in MCD an uncertainty	– Hypokalemia < 2 – Hyperkalemia > 10

Several assumptions are made in calculating the TTKG. First, in using the $(U/P)_{osm}$ to correct for water reabsorption in the MCD, one assumes that the majority of osmoles delivered to the MCD are not absorbed during transit. If a significant number of particles are absorbed in the MCD, for the same urine osmolality, one will underestimate the volume of water reabsorbed there, and hence the calculated $[K^+]_{CCD}$ will be higher than what it is in vivo. The major particles delivered to the MCD are urea and the electrolytes. In the absence of a marked degree of ECF volume contraction, the amount of urea and electrolytes reabsorbed in the MCD should not pose a problem [53].

Another assumption in the TTKG calculation is that an appreciable amount of K^+ is not secreted or reabsorbed in the MCD. Studies in normal rats showed that when samples of fluid were obtained from the beginning and the end of the MCD, there was little net change in the content of K^+ [54]. Although K^+ reabsorption has been observed in the MCD in K^+-deprived

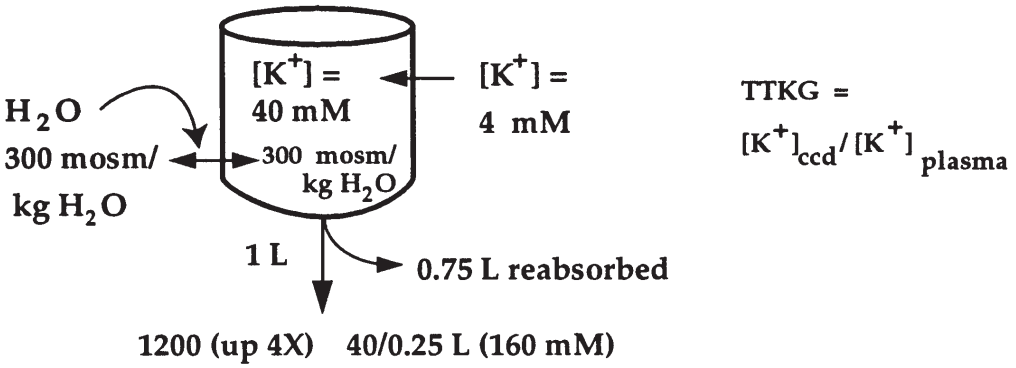

Figure 9. Effect of medullary water reabsorption on the urine [K^+]. The barrel-shaped structures represent the CCD, and the arrows below them represent the MCD. In the example, there is a high TTKG; i.e. the luminal [K^+] is 40 mM or 10 × the peritubular [K^+] of 4 mM. Consider what happens when 1 L of fluid traverses the MCD. In the example, 75% of the water is reabsorbed, but no K^+ is reabsorbed or secreted in the MCD. Therefore, the urine [K^+] is 4-fold higher (160 mM) as is the urine osmolality (1200 mOsm/kg H_2O). To correct for the rise in the urine [K^+] due to the reabsorption of water, we divide the urine [K^+] by 4, the ratio of the rise in urine osmolality between the terminal CCD and the final urine.

rats [55], these observations were made under conditions of profound K^+ depletion and may not apply in clinical conditions where the degree of K^+ depletion may be less severe. Similarly, K^+ secretion was demonstrated in the MCD in rats, but again under extreme conditions [56].

Keeping the above assumptions and pitfalls in mind, the TTKG can be used clinically to provide useful information about the role of the activity of the K^+ secretory process in the CCD in the pathogenesis of the disorders of K^+ homeostasis. The expected values for the TTKG under different stimuli are summarized in Table 2.

Possible Lesions to Explain a Higher than Expected [K^+] in the Lumen of the CCD

An unduly high [K^+] in the lumen of the CCD requires that the electrogenic reabsorption of Na^+ be augmented to generate a higher lumen-negative voltage in the CCD. From an ion channel analysis, this means that either there was faster reabsorption of Na^+ or slower reabsorption of Cl^- (Figure 7).

– *Relatively faster reabsorption of Na^+ in the CCD:* The clinical characteristics of a patient with a more open Na^+ channel are, on the Na^+ side, ECF volume expansion, low renin levels, and a tendency to hypertension in those individuals whose blood pressure is more sensitive to changes in volume than to vasoconstrictors (Figure 7). With ECF volume contraction, the urine could be free of Na^+ and Cl^-.

– *Relatively slower reabsorption of Cl^- in the CCD:* This may occur for 2 major reasons. For some patients, the following are required: a large delivery of Na^+ and Cl^- to the CCD and a stimulus to reabsorb these ions (ECF volume contraction) together with a capacity to reabsorb Na^+ faster than Cl^- in the CCD. For other patients, there is a decrease in the apparent permeability of the luminal membrane for Cl^-. Both of these groups of patients will have ECF volume contraction and hyperreninemia. They will not conserve Na^+ and Cl^- appropriately despite ECF volume contraction. Blood pressure

is not usually high despite a high level of the vasoconstrictor, angiotensin II (Ang II), because of the associated hypovolemia.

Possible Lesions to Explain a Lower than Expected [K^+] in the Lumen of the CCD

An unduly low [K^+] in the lumen of the CCD may indicate an inability to generate a favorable electrochemical gradient to promote secretion of K^+. From an ion channel analysis, this means a less electrogenic reabsorption of Na^+, either due to a more closed than usual ENaC, or a higher than usual permeability for Cl^- (or other anions) in the CCD. It is also conceivable that the defect may be one of a low open probability of the apical K^+ channels.

- *Relatively slower reabsorption of Na^+ in the CCD:* A low delivery of Na^+ to the CCD could possibly limit the secretion of K^+ (e.g. in a patient with a very marked degree of contraction of ECF volume and high rate of urea excretion). A relatively closed ENaC could diminish the ability to generate a favorable electrochemical gradient for the secretion of K^+ in the CCD and lead to hyperkalemia with a low [K^+] in the CCD. If the patient is particularly sensitive to vasoconstrictors, hypertension may develop [57]. Otherwise, a tendency to hypotension could be present, especially with a low salt diet. The other characteristics of this syndrome are a low ECF volume and renal Na^+ wasting. Renin levels will be high and there should be an inability to achieve an Na^+- and Cl^-- free urine when on a low salt diet (Table 1).
- *Relatively faster reabsorption of Cl^- in the CCD:* If this lesion were present, there would be an enhanced electroneutral rather than electrogenic absorption of Na^+ (Figure 4). Therefore, the cardinal features should be hyperkalemia, lower-than-expected TTKG that does not rise with the administration of exogenous mineralocorticoids, a tendency to an expanded ECF volume with low levels of renin, and possibly hypertension in those subjects whose blood pressure is particularly sensitive to an expanded ECF volume. These subjects should be able to have Na^+-and Cl^--poor urines and high plasma renin levels in response to ECF volume contraction. The induction of bicarbonaturia, however, can lead to a marked increase in the TTKG (if aldosterone is present) in these patients and we use this observation to support the speculation that there is a Cl^- shunt in the CCD [14, 26].
- *A low open probability of the luminal K^+ channel:* Other than in inherited diseases with a low ROM-K channel activity, there are no reports that specifically characterize this hypothetical lesion.

Molecular Studies

Recently the molecular basis of a number of the genetic disorders of hypokalemia and hyperkalemia has been identified. Therefore, characterization of the molecular defect can be carried out in the appropriate patients (Table 3, Figure 10).

Assess if Factors that Could Cause a Shift of K^+ Across Cell Membranes are Present

One should always ask whether a shift of K^+ across cell membranes is making the degree of hypokalemia or hyperkalemia more severe. If present, its basis should be explored.

Table 3. Hereditary Diseases and Hypokalemia.
All the disease categories present with hypokalemia and excessive excretion of K^+ associated with higher than expected urine [K^+]. Reproduced with permission [104].

	Gitelman's	Bartter's	Liddle's	GRA*	AME
Molecular lesion	Inhibited NaCl cotrans-porter in DCT	Inhibited NKCC, ROM-K channel, or basolateral Cl^- channel	Activated Na^+ channel in the CCD	Chimeric gene: ACTH driven mineralocorticoid synthesis	Defect in 11 β-HSDH in principal cells
Presenting feature	Tetany, unexpected lab finding	Failure to thrive, lab finding	Hypertension, hypokalemia, family history	Severe hypertension	Hypertension
Age of 1st symptoms	Teenage	Children	Young if severe	Young adult	Children
Mimicked by drugs	Thiazides	Loop diuretics	Amphotericin B	Mineralocorticoids	Licorice, carbenoxolone
Plasma Mg^{2+}	Low	Low	Normal	Normal	Normal
ECF volume	Low	May be low	High	High	High
Hypertension	No	No	Yes	Yes	Yes
Key diagnostic feature	Hypo-calciuria	Lower than expected maximum Uosm	Hypertension	Suppression of aldosterone by dexamethasone, excess cortisol and C-18 oxidation metabolites	Urine cortisone to cortisol ratio

*Some patients with this disorder do not have hypokalemia.
Abbreviations: GRA = glucocorticoid remediable aldosteronism, AME = Apparent mineralocorticoid excess, 11-βHSDH = 11 β hydroxysteroid dehydrogenase, TAL = Thick ascending limb of the loop of Henle, NKCC = Na^+, K^+, 2 Cl^- cotransporter in the TAL of the LOH.

Assess the Contribution of K^+ Intake

The plasma [K^+] can be maintained in the normal range despite wide fluctuations in K^+ intake. Nevertheless, variations in K^+ intake can contribute to the degree of hypokalemia or hyperkalemia if there is an underlying abnormality in the rate of excretion of K^+.

Specific Causes of Hypokalemia

A summary of the causes of hypokalemia is provided in Table 4 and Figure 11. We shall comment only briefly on some of these disorders, either because they are common or because new strides have been made in understanding their pathophysiology.

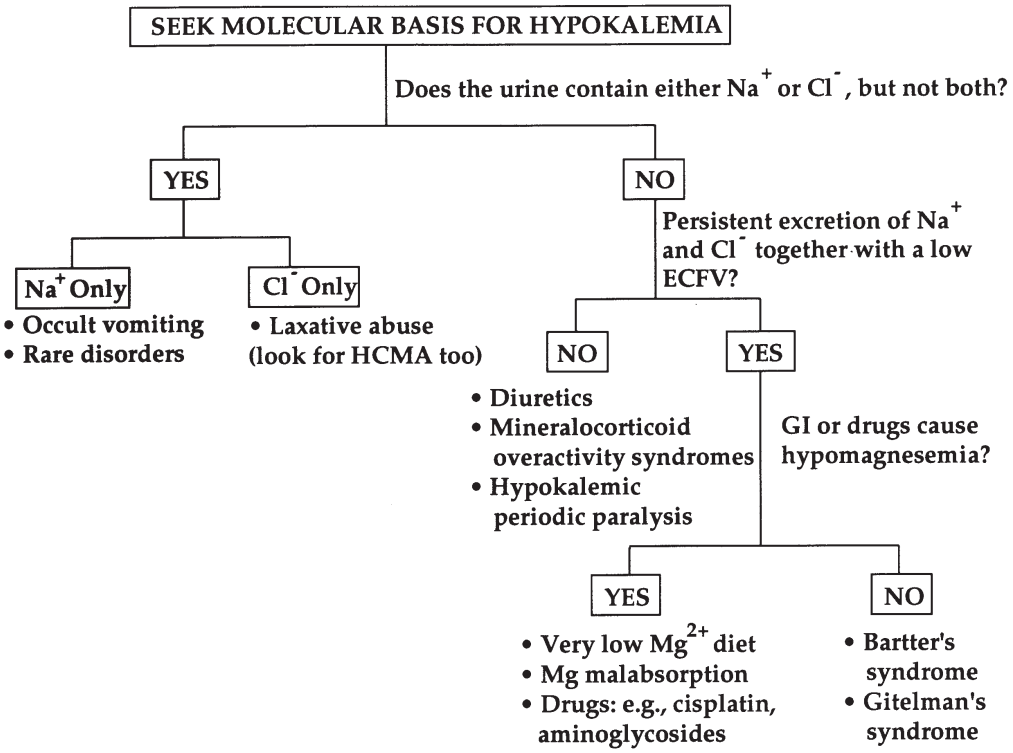

Figure 10. Differential diagnosis of hereditary causes of hypokalemia. The initial step is to rule out common causes of hypokalemia which may be denied by the patient. Here the urine electrolytes become very important (Table 1). A finding of persistent excretion of Na^+ and Cl^- despite a contracted ECF volume narrows the differential diagnosis to causes where there is obvious basis for hypomagnesemia or not. Finding Mg^{2+}-poor urine will suggest a low intake or poor GI absorption of Mg^{2+}. Failure to find an obvious cause for renal Mg^{2+} wasting suggests that Bartter's or Gitelman's syndrome may be present. Reproduced with permission [104].

Disorders with Hypokalemia and a Low ECF Volume

Diuretic-induced Hypokalemia

– *Underlying pathophysiology:* Two factors contribute to the development of hypokalemia in patients receiving diuretics: a high rate of flow in CCD and an increased net secretion of K^+ due to the effect of aldosterone (released in response to a low ECF volume).

– *Clinical features:* Hypokalemia is usually modest in degree. A fall in plasma $[K^+]$ to < 3 mM is observed in < 10% of patients, usually within the first 2 weeks of therapy [58].

– *Diagnosis requirement:* One must ask if the patient has been taking diuretics. At times, abuse of diuretics may be denied, so screening the urine for diuretics may be needed (choose a urine when diuretics are acting, i.e. one which contains appreciable Na^+ and Cl^-).

– *Differential diagnosis:* If diuretic abuse is firmly denied by the patient, a diagnosis of Bartter's or Gitelman's syndrome may be suspected because the urine will

Table 4. Causes of Hypokalemia

I. Decreased intake of K^+

II. Shift of K^+ into cells
- Hormones: Insulin, sympathomimetics
- Gain of anions in the intracellular fluid (recovery phase of ketoacidosis, refeeding after cachexia, treatment of pernicious anemia)
- Metabolic alkalosis
- Others: Hypokalemic periodic paralysis.

III. Intestinal loss of K^+
- Diarrhea, ileus

IV. Excessive loss of K^+ in urine
1. **High flow CCD**, e.g. diuretics, genetic disorders with inhibition of Na^+-transport (Bartter's syndrome or Gitelman's syndrome).
2. **High $[K^+]_{CCD}$**

A) Disorders leading to a relatively "faster Na^+" in the CCD
- High aldosterone, high renin: Low effective circulating volume (diuretics, vomiting, diarrhea), malignant hypertension, renal artery stenosis, renin-secreting tumor
- High aldosterone, low renin: Adrenal adenoma or bilateral adrenal hyperplasia, glucocorticoid remediable aldosteronism
- Low aldosterone, low renin: Decreased 11-βHSDH activity (apparent mineralocorticoid excess syndrome), inhibition of 11-βHSDH (e.g. licorice, carbenoxolone, swallowed chewing tobacco), very high levels of glucocorticoids (e.g. ACTH-producing tumor), increased activity of ENaC (Liddle's syndrome, drugs: amphotericin B)

B) Disorders leading to a relatively "slower Cl^-" in the CCD
- Bicarbonaturia: Vomiting, use of acetazolamide, distal RTA, patients with proximal RTA treated with alkali.
- Hypomagnesemia.

often contain abundant Na^+ and Cl^- in both settings. Diuretic abuse should be suspected if even one spot urine has little Na^+ and Cl^- reflecting the normal renal response to low ECF volume (Table 1). This diagnosis can be confirmed by screening a urine sample with abundant Na^+ and Cl^- for diuretics. The urine electrolytes also provide clues to the differential diagnosis in patients with hypokalemia due to diuretic abuse from those with hypokalemia due to occult vomiting or the abuse of laxatives. In the occult vomiter, the key finding is a very low urine $[Cl^-]$ (Table 1). In the laxative abuser with a contracted ECF volume, the urine $[Na^+]$ will be low, but the urine $[Cl^-]$ may be high if there is a high rate of excretion of NH_4^+ in response to the hyperchloremic metabolic acidosis (Table 1).

– *Molecular basis:* None.

– *Therapy:* Some of the issues discussed here under treatment of diuretic-induced hypokalemia will apply to the treatment of other settings with hypokalemia. Specific issues related to therapy of diuretic-induced hypokalemia will also be addressed.

Whether a mild degree of hypokalemia should be treated is debatable. Since patients with ischemic heart disease, those with left ventricular hypertrophy, and those treated with digitalis may be at increased risk for arrhythmias, even a mild degree of hypokalemia should be avoided in these patients. While it is generally stated that a fall in plasma $[K^+]$ from 4 to 3 mM indicates a total body deficit of 200 – 400 mmol of K^+ and may be as much as 800 mmol if plasma $[K^+]$ falls to 2 mM [59]; this is not a useful quantitation in any individual patient. Factors that may induce a shift of K^+ into the ICF compartment may also be present, and it is not possible to determine the magnitude of the total body deficit of K^+ based on the value of plasma $[K^+]$. The bottom line is that careful monitoring of plasma $[K^+]$ is required as the K^+ deficit is being repleted. Two other issues bear mentioning. First, with chronic hy-

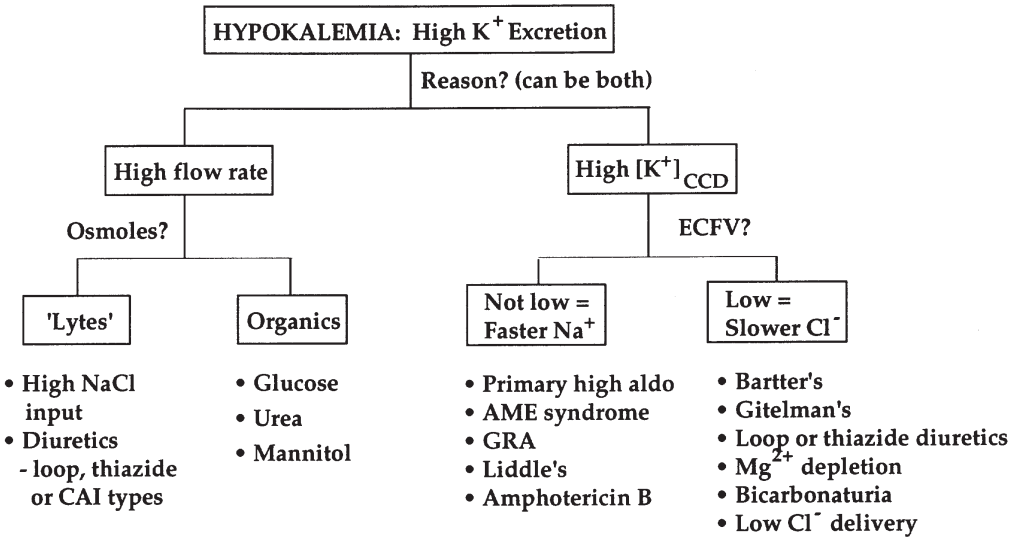

Figure 11. Approach to the patient with hypokalemia. The causes for excessive excretion of K^+ (> 15 – 20 mmol/day) despite hypokalemia are too high a flow rate in the CCD (left limb) and/or too high a $[K^+]$ in the lumen of the CCD (right limb). Both flow rate and $[K^+]_{CCD}$ should be evaluated in each patient. Final considerations are shown by the bullet symbols. A slower Cl^- reabsorption in the CCD is suggested by high plasma renin activity and NaCl wasting despite low ECF volume; the converse applies for faster Na^+ reabsorption. Reproduced with permission [104]. Abbreviations: CAI = Carbonic anhydrase inhibitor type of diuretic, AME = Apparent mineralocorticoid excess, GRA = Glucocorticoid-remedial aldosteronism.

pokalemia, the CCD may become hyporesponsive to the kaliuretic effect of aldosterone and thus there is a risk for the development of hyperkalemia during K^+ replacement [60, 61]. Second, patients who have disorders, or are taking drugs that may impair their ability to shift K^+ into cells or to excrete K^+ in the urine, may be particularly at risk of developing hyperkalemia with therapy.

In the absence of conditions that may limit the oral intake of K^+ or its absorption by the gut (e.g. vomiting, ileus or the absence of bowel sounds), the oral route is usually preferred. At times, however, the urgency of treatment may necessitate using the IV route. When using a peripheral vein, the $[K^+]$ in the infusate should not exceed 40 mM, as higher $[K^+]$ may irritate small veins and cause painful phlebitis. In general, the rate of K^+ administration should not exceed 60 mmol/hour.

Since patients with diuretic-induced hypokalemia have both K^+ and Cl^- deficits, K^+ should be given as its Cl^- salt. In general, tablets are better tolerated than the liquid form. Most tablets are slow-release preparations, either microencapsulated or in wax matrix, which have occasionally caused ulcerative or stenotic gastrointestinal lesions. A salt substitute may be an inexpensive and generally well-tolerated form of K^+ supplementation (Co-salt provides 14 mmol of K^+ per gram). Contrary to customary belief, increasing intake of K^+-rich food (e.g. bananas) is not an effective way to replace a K^+ deficit. Bananas provide little K^+, only about 1 mmol per inch.

Some particular issues about hypokalemia

and diuretic use are worth highlighting. First, because the risk of development of hypokalemia is dose-dependent and because increasing the dose of hydrochlorothiazide beyond 12.5 – 25 mg does not usually result in further benefit in terms of blood pressure control, the lowest effective dose of this drug should be used. Second, the degree of renal wasting of K^+ can be minimized by restricting NaCl intake to 100 mmol/day. Third, the use of K^+-sparing diuretics provides an effective way of reducing the renal loss of K^+. The ENaC blockers (amiloride and triametrene) are generally better tolerated and lack the gastrointestinal and hormonal side effects (impotence, decreased libido, amenorrhea, gynecomastia) that may occur with the aldosterone competitive inhibitor spironolactone. The availability of combination tablets of hydrochlorothiazide with amiloride or triametrene also makes compliance less of an issue. These drugs, however, blunt the renal response to an increase in the plasma $[K^+]$ and also have a long half-life. Therefore they should be used cautiously in patients on β-blockers, angoitensin-converting enzyme (ACE) inhibitors, or nonsteroidal anti-inflammatory drugs (NSAID) and those with an underlying renal disease.

Vomiting-induced Hypokalemia

– *Underlying pathophysiology:* Because the $[K^+]$ in gastric fluid is usually < 15 mM, hypokalemia in patients with vomiting or nasogastric suction results primarily from the loss of K^+ in the urine. Aldosterone is released in response to Ang II that is formed because of ECF volume contraction. Aldosterone leads to a more open ENaC in the CCD (Figure 5). Delivery of HCO_3^- to the lumen of CCD is the result of a transient rise in its concentration in plasma due to vomiting (Figure 12). A higher distal delivery of HCO_3^- causes a higher net secretion of K^+ (Figure 13 and [34, 37]). To a lesser extent, hypokalemia may be the result of a shift of K^+ into the ICF compartment due to the alkalemia. Once the degree of hypokalemia becomes more severe, the rate of K^+ excretion declines, but not to the very low rates in otherwise normal subjects consuming a low-K^+ diet [50].

– *Clinical features:* Hallmarks are a significant degree of hypokalemia, metabolic alkalosis, and a very low $[Cl^-]$ in the urine (Table 1). In a patient with recent vomiting, the urine may contain an abundant Na^+ despite ECF volume contraction because the excretion of HCO_3^- obligates the excretion of Na^+.

– *Diagnosis requirement:* Key elements are a history of vomiting, a significant degree of hypokalemia, metabolic alkalosis, and a very low $[Cl^-]$ in the urine (Table 1). The use of urine electrolytes may help reveal the basis for hypokalemia in a patient with occult vomiting.

– *Differential diagnosis*: If the patient denies vomiting, other causes of hypokalemia with a low ECF volume must be considered (Table 4).

– *Molecular basis:* None.

– *Therapy:* Therapy is directed towards the underlying cause of vomiting and the administration of K^+. Again, these patients also have a deficit of Cl^-. K^+ should be administered as its Cl^- salt along with NaCl as needed.

Hypokalemia in Patients with Hyperchloremic Metabolic Acidosis

– *Pathophysiology:* The 2 major entities to consider in these patients are distal RTA due to a low rate of H^+ secretion in the

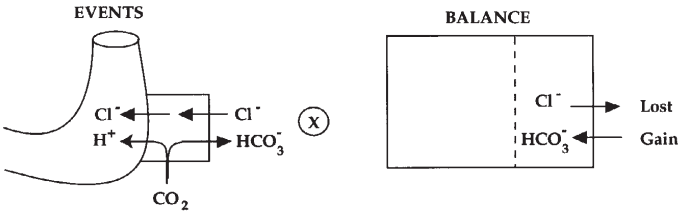

Figure 12. H^+ Secretion in stomach and mass balance for H^+. The structure on the left represents a parietal cell in the stomach. There is an net gain of HCO_3^- and a loss of Cl^- from the ECF compartment when HCl is secreted. Reproduced with permission [104] of the authors.

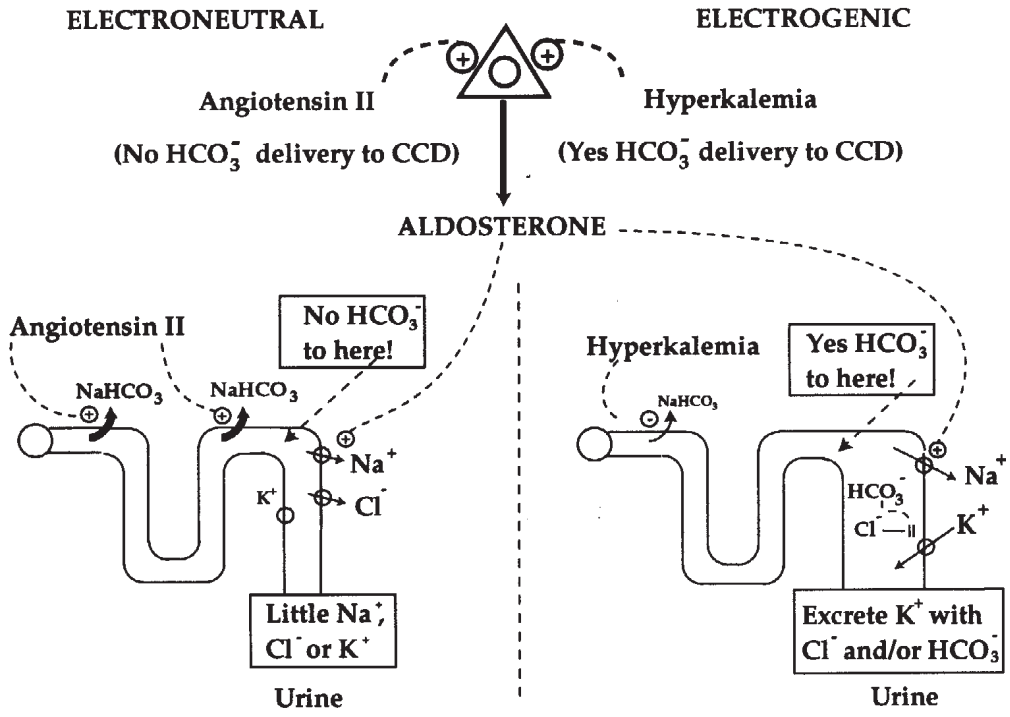

Figure 13. Aldosterone and the augmented reabsorption of NaCl. The adrenal gland is depicted by the triangular structure. The secretagogue on the left for the release of aldosterone is angiotensin II. Angiotensin II, by stimulating the reabsorption of HCO_3^- in the proximal and distal convoluted tubules, diminishes the delivery of HCO_3^- to the CCD and thereby a kaliuresis is not promoted. The secretagogue on the right for the release of aldosterone is K^+. Hyperkalemia, by inhibiting the reabsorption of HCO_3^- in the proximal convoluted tubule, increases the delivery of HCO_3^- to the CCD and thereby a kaliuresis is promoted. Reproduced with permission [104].

distal nephron and loss of $NaHCO_3$ via the gastrointestinal (GI) tract. For the former, the key element in the pathophysiology of their hypokalemia is the retention of HCO_3^- in the lumen of the CCD. In the latter, loss of K^+-rich colonic fluids (especially from distal colon) can lead directly to hypokalemia. In some cases of diarrhea, however, the degree of hypokalemia is modest. The reason is that al-

though the presence of aldosterone (due to ECF volume contraction) causes the ENaC in the CCD to be open, limited delivery of HCO_3^- to the CCD (low filtered HCO_3^- due to metabolic acidosis plus the effects of Ang II, metabolic acidosis, and hypokalemia to enhance proximal reabsorption of HCO_3^- [37]) leads to electroneutral reabsorption of Na^+ in the CCD. Therefore, aldosterone acts as an NaCl-retaining rather than a kaliuretic hormone (Figure 13).

– *Clinical picture:* Hypokalemia with hyperchloremic metabolic acidosis.
– *Diagnosis requirement:* In patients with distal RTA due to a low rate of H^+ secretion in the distal nephron, there is a low rate of NH_4^+ excretion and a relatively high urine pH (about 6.5) (see chapter I-3 on *Acid-base Balance* for more details). In patients with a GI problem, a history of a diarrheal illness may be obtained. Abuse of laxatives, however, may be firmly denied. If suspected, measurement of the urine electrolytes may provide helpful clues. The urine $[Na^+]$ will be low if the ECF volume is contracted, but the $[Cl^-]$ in the urine is characteristically high reflecting the high rate of NH_4^+ excretion in response to metabolic acidosis (Table 1). At times, one might have to rely on measurements of stool electrolytes and other evidence for laxatives in the stool to confirm the diagnosis.
– *Differential diagnosis:* Other causes of hypokalemia with a low ECF volume are illustrated in Table 4.
– *Molecular basis:* Usually this is not an issue.
– *Therapy:* Because these patients have hypokalemia and metabolic acidosis, K^+ can be given with HCO_3^- or other anions that can be metabolized to HCO_3^- (e.g. citrate). Nevertheless, because the administration of HCO_3^- may cause the shift of K^+ into the ICF compartment, K^+ should be replaced for the most part as its Cl^- salt early in therapy.

Bartter's and Gitelman's Syndromes

– *Pathophysiology: The pathophysiology of Bartter's syndrome can be thought of as having a loop diuretic acting 24 hours a day. The pathophysiology of Gitelman's syndrome can be thought of as having a thiazide diuretic acting 24 hours a day.*

  The high rate of K^+ excretion in both disorders has 2 components: a high flow rate in CCD and a high $[K^+]$ in the lumen of the CCD. The high flow rate in the CCD is due to the very large delivery of Na^+ and Cl^-, the result of their inhibited reabsorption in upstream nephron segments (Figure 3). The high $[K^+]$ in the lumen of the CCD is due to a relatively faster rate of reabsorption of Na^+ relative to that of Cl^-. The rate of Na^+ reabsorption is stimulated because of the contraction of the ECF volume, one of the hallmarks of the clinical picture. Hypomagnesemia may contribute to the pathophysiology of renal K^+ wasting, especially in patients with Gitelman's syndrome [62].
– *Clinical picture:* These uncommon disorders are characterized by ECF volume contraction due to renal salt wasting, hypokalemia, and metabolic alkalosis (Table 4). Hypomagnesemia is more consistently seen in patients with Gitelman's syndrome. While hypercalciuria is found in many patients with Bartter's syndrome, an extreme degree of hypocalciuria

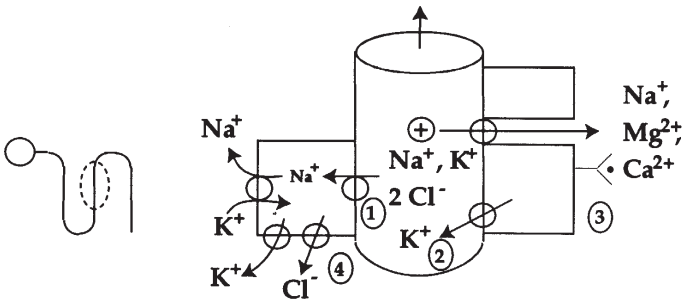

Figure 14. Possible lesions for Bartter's syndromes. A stylized nephron is shown on the left with the thick ascending limb of the loop of Henle (LOH) shown by the dashed oval. The structure to the right represents an enlargement of the thick ascending limb of the LOH. The possible lesions are the Na^+-K^+-2 Cl^- cotransporter (site 1), the luminal K^+ channel (site 2), occupation of the basolateral Ca^{2+} receptor by a cationic ligand (site 3), or the Cl^- channel in the basolateral membrane (site 4).

is a characteristic finding in almost all patients with Gitelman's syndrome [62]. In contrast to patients with Bartter's syndrome, patients with Gitelman's syndrome should have the ability to elaborate a maximally concentrated urine when ADH acts, unless there is another lesion that caused renal medullary damage as chronic hypokalemia or the chronic use of drugs that might damage this area of the kidney such as NSAIDs.

– *Diagnosis requirement:* The presence of hypokalemia with renal salt wasting and persistently elevated [Na^+] and [Cl^-] in the urine is the hallmark of the diagnosis (Table 1).
– *Differential diagnosis:* The major differential diagnosis is with patients with diuretic abuse, laxative abuse, or occult vomiting. The use of urine electrolytes in this differential diagnosis is a critical step (Table 1).
– *Molecular basis:* Patients with Bartter's syndrome seem to represent a heterogeneous group with regard to the molecular lesions (Table 3, Figure 14). Mutations that cause a loss of function have been identified in the genes encoding for the bumetonide-sensitive Na^+-K^+-2 Cl^- co-transporter [63], the luminal K^+ channel (ROM-K) [64], and the Cl^- channel in the basolateral membrane of the thick ascending limb of the loop of Henle [65]. Those patients with a ROM-K channel defect may have their initial presentation as hyperkalemia and NaCl wasting because ROM-K is the major K^+ channel in principal cells of the CCD. The biochemical findings evolve to the more typical ones of hypokalemia and metabolic alkalosis with time.

  The vast majority of patients with Gitelman's syndrome have mutations in the gene encoding the NaCl co-transporter in the early distal convoluted tubule [66]. Nevertheless, some patients have all the clinical characteristics of Gitelman's syndrome without a recognized mutation in this transporter [67].
– *Therapy:* Correction of hypokalemia is extremely difficult in these patients, even with large supplements of K^+. Hypomagnesemia seems to be an important factor in the enhanced kaliuresis in some, but not all patients with Gitelman's syndrome. Correction of hypomagnesemia with

oral magnesium is usually limited by gastrointestinal side effects. K^+-sparing diuretics may help conserve K^+ but they may also exacerbate renal salt wasting. ACE inhibitors have been tried in some patients with variable success, but hypotension is a major concern with this therapy. We are concerned about the prolonged use of NSAIDs because of the potential for chronic renal dysfunction.

Hypokalemia Due to Cationic Drugs Like Gentamicin

- *Pathophysiology:* Gentamicin is an antibiotic that has the capacity to bind to a receptor for Ca^{2+} on the basolateral aspect of cells of the thick ascending limb of the loop of Henle (Figure 14) [68]. This binding of gentamicin leads to inhibition of the luminal K^+ channel (ROMK), and thereby to furosemide-like effects. Therefore, the pathophysiology of gentamicin-induced hypokalemia can be thought of as having a loop diuretic acting 24 hours a day. The high rate of excretion of K^+ has 2 components: a high flow rate in the CCD and a high [K^+] in the lumen of the CCD. The high [K^+] in the lumen of the CCD is due to a faster rate of Na^+ reabsorption relative to that of Cl^-. Hypomagnesemia may contribute to the pathophysiology of renal K^+ wasting in these patients. A similar story might apply for other drugs that bind to the Ca^{2+} receptor in the loop of Henle such as cisplatin.
- *Clinical picture:* This disorder is characterized by ECF volume contraction due to renal salt wasting, polyuria, a fall in the glomerular filtration rate (GFR), hypokalemia, hypomagnesemia, hypercalciuria, and metabolic alkalosis.
- *Diagnosis requirement:* The presence of the features outlined above in a patient receiving gentamicin or drugs with a similar effect.
- *Differential diagnosis:* All the conditions described above must be considered.
- *Molecular basis:* None.
- *Therapy:* Discontinue the drug. Wait for its side effects to wear off, but this may take a considerable amount of time. Supportive therapy with Na^+, K^+, and Mg^{2+} should be given if the patient is symptomatic and in danger from these deficits.

Disorders with Hypokalemia and a Normal or High ECF Volume

Primary Hyperaldosteronism

- *Pathophysiology:* Hypersecretion of aldosterone due to an adrenal adenoma or bilateral adrenal hyperplasia.
- *Clinical Picture:* This diagnosis should be suspected in patients with hypertension and unexplained hypokalemia with renal K^+ wasting. Nevertheless, hypokalemia is not a universal finding in these patients [69].
- *Diagnosis requirement:* The diagnosis hinges on the finding of an elevated plasma aldosterone level and a very low plasma renin activity. A random plasma aldosterone to plasma renin activity ratio is a sufficient screening test [70]. The next step is to differentiate patients with adrenal adenoma from those with bilateral adrenal hyperplasia. This can be usually achieved with computed tomography (CT) or magnetic resonance imaging (MRI). If an adrenal adenoma is not detected, adrenal vein sampling or an iodocholesterol scan can be used to distinguish between these 2 possibilities [71].

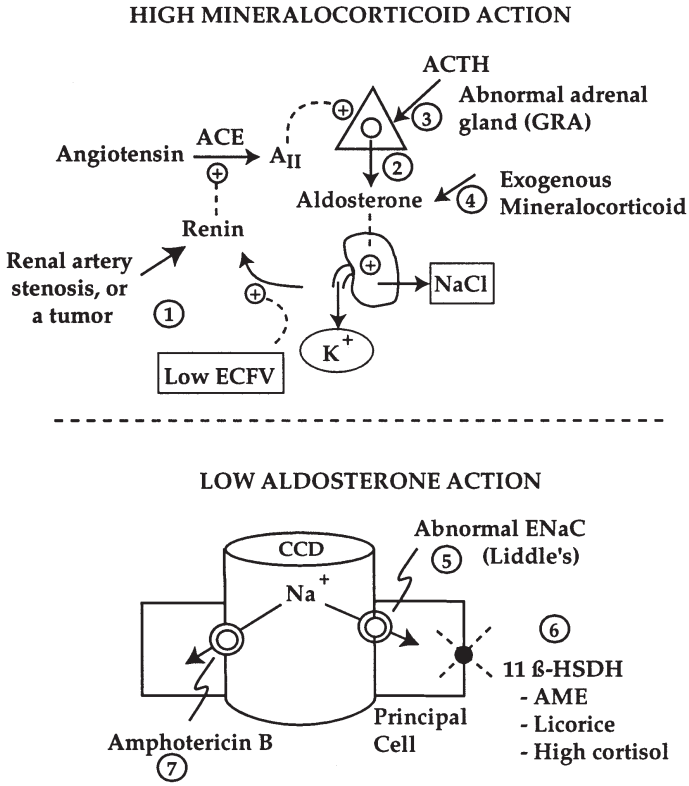

Figure 15. Differential diagnosis of the patient with hypokalemia. There are 7 causes for high mineralocorticoid action identified in this figure with the following numbers. Reproduced with permission [104].
A) Those with high mineralocorticoid action: 1. High renin (e.g. renal artery stenosis, renin producing tumors). 2. Cells (e.g. adenoma) in the adrenal cortex produce aldosterone or a compound with mineralocorticoid bioactivity. 3. ACTH stimulates aldosterone production because there is a genetic lesion in the adrenal gland in which the ACTH promoter drives the synthesis of a compound with mineralocorticoid bioactivity. Suppressing ACTH with glucocorticoids decreases their production (GRA, a genetic chimera). 4. Exogenous compounds mimicking the actions of aldosterone such as fludrocortisone.
B) Those with low mineralocorticoid action: 5. An epithelial ENaC in the luminal membrane which is permanently in an open conformation due to a mutation (Liddle's syndrome). 6. Blocking the destruction of cortisol in principal cells by creating a relatively low activity of 11 β-HSDH (e.g. licorice). 7. Insertion of an artificial Na^+ channel in the luminal membrane of the CCD (e.g. amphotericin B).

– *Differential Diagnosis:* The finding of very low plasma renin activity (PRA) with high plasma aldosterone levels separate patients with primary hyperaldosteronism from those with other causes of hypertension and hypokalemia (Figure 15, Tables 3 and 4). Patients with glucocorticoid remediable aldosteronism (GRA), however, also have elevated plasma aldosterone levels with suppressed PRA. These patients typically have the onset of hypertension in early adulthood and a strong family history of hypertension, cardiovascular, and cerebrovascular events. The hypersecretion of aldosterone in these patients is suppressed with the

administration of dexamethasone. Patients with GRA also have marked hypersecretion of 18-hydroxycortisol and 18-oxocortisol in their urine.

– *Therapy:* In patients with an adrenal adenoma, unilateral adrenalectomy is usually the preferred treatment. In patients with bilateral adrenal hyperplasia and those with adrenal adenomas who are not candidates for surgery, medical therapy with K^+-sparing diuretics is recommended. Amiloride is generally better tolerated than spironolactone.

Glucocorticoid Remediable Aldosteronism (GRA)

– *Pathophysiology:* GRA is a rare form of adrenal hyperplasia in which aldosterone secretion is regulated exclusively by ACTH [72]. There is also marked overproduction of C-18 oxidation products of cortisol, 18-hydroxycortisol, and 18-oxocortisol.

– *Clinical picture:* The onset of severe hypertension may occur in early adulthood. There is often a strong family history of hypertension and early onset of cardiovascular and cerebrovascular diseases. Interestingly, hypokalemia is not present in a significant number of these patients.

– *Diagnosis requirement:* The diagnosis hinges on demonstrating suppression of aldosterone with the administration of glucocorticoids (dexamethasone or prednisone), detection of very high levels of C-18 oxidation products of cortisol in the urine [73], and ultimately, genetic testing to detect the chimeric gene.

– *Differential diagnosis:* One must rule out other causes of hypertension and unexplained hypokalemia (Figure 15). The characteristic features for the diagnosis of GRA were discussed previously.

– *Molecular basis:* This disorder is due to a chimeric gene in which the regulatory region of the gene encoding for the enzyme P-450 (the zona fasciculata enzyme required for the synthesis of cortisol) is linked to the coding sequence of the gene for the enzyme P-450, 18-C (the zona glomerulosa enzyme required for the synthesis of aldosterone) [72]. Therefore, secretion of aldosterone is exclusively regulated by ACTH. Also, because of an apparent expression of this enzyme in the zona fasciculata, cortisol (a C-17 hydroxylated steroid) also becomes hydroxylated at the C-18 position, leading to the production of cortisol-aldosterone hybrid compounds.

– *Therapy:* Administration of glucocorticoids (dexamethasone or prednisone) corrects the hypersecretion of aldosterone by suppressing ACTH.

ACTH-Producing Tumor or Severe Cushing Syndrome

– *Pathophysiology:* The clinical picture is similar to hyperaldosteronism, but the level of aldosterone in plasma is low. Because of an overabundance of cortisol, the activity of the two 11 β-HSDH enzymes probably fail to inactivate all the cortisol that enters principal cells (Figure 6). As a result, cortisol binds to the mineralocorticoid receptor and exerts mineralocorticoid activity.

– *Clinical picture:* ACTH overproduction is commonly seen in patients who have oat cell carcinoma of the lung. In patients with ACTH-producing tumors, overt signs of glucocorticoid excess may not be evident at the time of diagnosis. The plasma $[K^+]$ is often very low.

– *Diagnosis hinges on:* One must demonstrate very elevated plasma cortisol levels. Plasma ACTH levels will be high if there is an ACTH-producing tumor and markedly suppressed in patients with Cushing syndrome.
– *Differential diagnosis:* A similar clinical picture can be induced with primary aldosteronism, GRA, Liddle's syndrome and chronic ingestion of licorice or licorice-like compounds (such as carbenoxolone or chewing tobacco) [74].
– *Molecular basis:* None.
– *Therapy:* Therapy is directed at the primary disorder. For treatment of hypokalemia, large supplements of KCl and drugs that inhibit ENaC are often necessary.

Syndrome of Apparent Mineral Corticoid Excess (AME)

– *Pathophysiology:* The clinical picture is of hyperaldosteronism, but the level of aldosterone in plasma is low. Because of decreased activity of the enzyme 11 β-HSDH, cortisol binds to the mineralocorticoid receptors and exerts mineralocorticoid activity [75].
– *Clinical picture:* One finds an autosomal recessive disorder of juvenile hypertension and hypokalemia.
– *Diagnosis requirement:* The demonstration of suppressed plasma aldosterone and PRA without excess cortisol secretion (Figure 15). The diagnosis is confirmed by finding of an elevated urinary cortisol: cortisone ratio.
– *Differential diagnosis:* A similar clinical picture can be induced with chronic ingestion of licorice or licorice-like compounds (such as carbenoxolone or chewing tobacco). The active moiety in these compounds is glycyrrhetinic acid, which inhibits the 11 β-HSDH.
– *Molecular basis:* Several mutations in the gene that encodes for the kidney isoform of the enzyme 11 β-HSDH have been identified [76]. These mutations result in decreased enzyme activity and thus impaired inactivation of cortisol.
– *Therapy:* The administration of dexamethasone, which does not bind the mineralocorticoid receptor, helps to correct the hypertension and hypokalemia by suppressing endogenous cortisol production.

Liddle's Syndrome

– *Pathophysiology:* The clinical picture is of hyperaldosteronism, but the level of aldosterone is low. The pathophysiology of this disorder is one of a constitutively active ENaC in the CCD [77].
– *Clinical picture:* One finds an autosomal dominant inherited disorder of early onset of severe hypertension and hypokalemia.
– *Diagnosis requirement:* A positive family history of early onset hypertension and hypokalemia, very low plasma aldosterone levels and PRA are key elements in the diagnosis (Figure 15). There is no excess secretion of cortisol, and the urine cortisol to cortisone ratio is not elevated. Control of hypertension and correction of hypokalemia are more likely achieved with the administration of ENaC blockers (amiloride) rather than with mineralocorticoids antagonist (spironolactone).
– *Differential diagnosis:* Other causes of hypertension and hypokalemia, the distinguishing features of Liddle's syndrome were mentioned above.

– *Molecular basis:* Several mutations in the gene encoding for ENaC have been described in patients with this syndrome [78]. Some of these mutations resulted in truncation of the cytoplasmic regions of the β- or α-subunits of the ENaC complex. Other mutations involved a missense mutation in the proline-rich region of these subunits; hence these regions seem to be critical in the interaction between ENaC and cytoskeletal elements such as Nedd 4 protein [79]. As a result of these mutations, there seems to be decreased retrieval of the ENaC from the luminal membrane.
– *Therapy:* The administration of amiloride or triametrene, drugs that directly block the ENaC, is the best medical therapy.

Hypokalemia Due to Drugs Like Amphotericin B

– *Pathophysiology:* The pathophysiology of amphotericin B-induced hypokalemia can be thought of as having an ENaC-like channel which is permanently in an open configuration in the CCD. The high rate of K^+ excretion is due to a relatively high [K^+] in the lumen of the CCD, the result of a faster rate of Na^+ reabsorption relative to that of Cl^-.
– *Clinical picture:* The clinical picture is predominantly due to the underlying illness that necessitates the administration of amphotericin B. Hypokalemia is usually associated with a normal or expanded ECF volume (Figure 15).
– *Diagnosis requirement:* The presence of the features outlined above in a patient receiving amphotericin B.
– *Differential diagnosis*: All the conditions described above must be considered.
– *Molecular basis:* The lesion is due to the insertion of an artificial, unregulated ENaC.
– *Therapy:* Treat the underlying illness, discontinue the drug if the side-effects are life threatening, and wait for its side effects to wear off. Take measures to decrease the flow rate in the CCD when amphotericin B is acting.

Hypokalemic Periodic Paralysis

– *Pathophysiology:* Episodes of transient shift of K^+ from the ECF to the ICF.
– *Clinical Picture:* The dominant finding is recurrent, transient episodes of muscle weakness that may progress to paralysis in association with hypokalemia. Hypokalemia may be severe at times (< 2.0 mM). Characteristically, the attacks occur after a large carbohydrate meal, strenuous exercise, or the administration of insulin. A variant of this disorder occurs in Asians and is associated with thyrotoxicosis. The idiopathic variety is inherited as an autosomal dominant disorder and usually manifests in the teenage years.
– *Diagnosis requirement:* The diagnosis hinges on finding the characteristic clinical picture and is confirmed by molecular studies.
– *Molecular basis:* In patients with this disorder, the RMP is 10 – 15 mvolts less negative than in normal muscle fibers even if the plasma [K^+] is normal. The basis of this does not seem to be a problem with the voltage-gated Na^+ channel as in patients with hyperkalemic periodic paralysis [80, 81]. Genetic analysis has suggested that the abnormality in patients with hypokalemic periodic paralysis is linked to the gene that encodes for the

Table 5. Causes of Hyperkalemia

I. Pseudohyperkalemia:
- – Tight tourniquet, fist clenching
- – Thrombocytosis with megakaryocytes
- – High WBC count

II. Excess intake of K^+ (in patients with impaired renal excretion of K^+).

III. Shift of K^+ from the ICF to the ECF:
- – Catabolism (rhabdomyolysis, tumor lysis syndrome)
- – Metabolic acidosis (acute phase of inorganic acidosis)
- – Drugs (digitalis, depolarizing agents)
- – Fasting hyperkalemia (dialysis patients)
- – Hyperkalemic periodic paralysis

IV. Decreased K^+ excretion (renal failure):

A. Decreased flow in the CCD:
- – Low rate of excretion of osmoles (malnutrition)

B) Decreased luminal negativity in the CCD:

i) Disorders leading to relatively "slow Na" in the CCD:
- – Chronic renal failure
- – Low renin: Damage to, or synthetic defect in, JG apparatus
- – Low aldosterone: Hyporeninemia, damage to adrenal glands (autoimmune disorder, granulomatous disease), defect in aldosterone biosynthesis; congenital or acquired (heparin, ketoconozole), decreased aldosterone binding to its receptor (competitive inhibition by spironolactone)

ENaC defect: Type I pseudohypoaldosteronism, drugs that block the ENaC (amiloride, triamterene, trimethoprim, pentamidine).

ii) Disorders leading to a relatively "fast Cl" in the CCD:
- – Gordon's syndrome
- – A subgroup of the patients with hyporeninemic hypoaldosteronism
- – Cyclosporin A.

dihydropyridine-sensitive Ca^{2+} channel in skeletal muscles [82]. It is not clear how this leads to the effects on RMP and plasma $[K^+]$.

– *Therapy:* Therapy for this disorder is largely symptomatic or empirical. Hyperthyroidism, if present, is treated in the usual fashion. Patients are advised to avoid carbohydrate-rich meals and vigorous exercise. Nonselective β-blockers may reduce the number of the attacks and the severity of fall in plasma $[K^+]$ during an attack. Acetazolamide 250 – 750 mg/day has been used successfully in some patients, although the basis of its beneficial effect is unclear. An acute attack is treated with the administration of KCl. There is, however, the risk of post-treatment hyperkalemia as K^+ move back into the ECF.

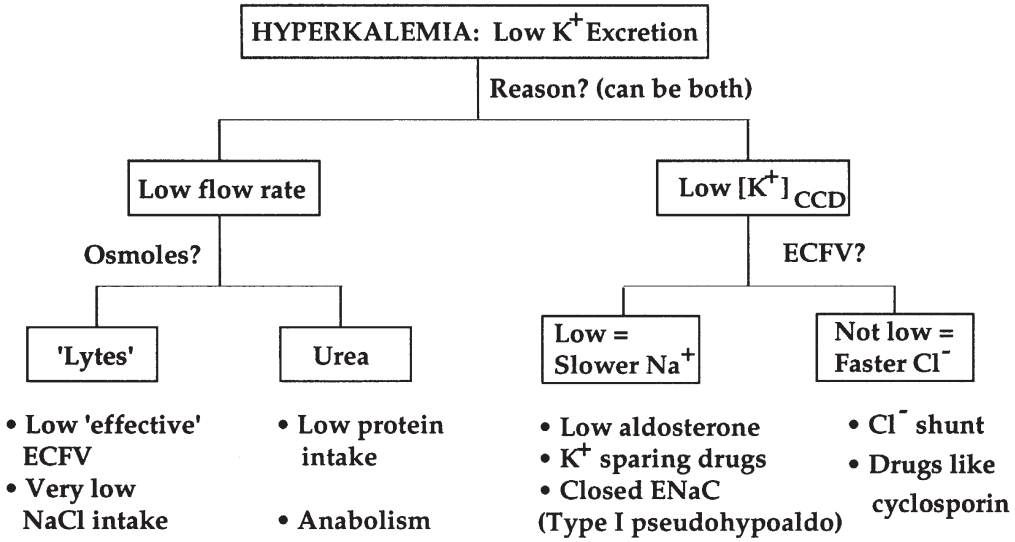

Figure 16. Approach to the patient with hyperkalemia. The causes for a low rate of excretion of K^+ (< 200 mmol/day) despite hyperkalemia are too low a flow rate in the CCD (left limb) and too low a $[K^+]$ in the lumen of the CCD (right limb). Both flow rate and $[K^+]_{CCD}$ should be evaluated in each patient. Final considerations are shown by the bullet symbols. A slower Na^+ reabsorption is suggested by high renin and NaCl wasting despite low ECF volume; the converse applies for faster Cl^- reabsorption. In some cases of renal failure, the excessive flow rate per nephron limits electrogenic reabsorption of Na^+ and thereby behaves as if there is relatively slower reabsorption of Na. Reproduced with permission [104].

Specific Causes of Hyperkalemia

A list of the causes of hyperkalemia based on their possible underlying pathophysiology is provided in Table 5. An algorithm of the clinical approach to these patients is in Figure 16.

Addison Disease

– *Pathophysiology:* The lack of aldosterone leads to "closed" ENaC in CCD.
– *Clinical picture:* The most common cause of this disorder used to be bilateral adrenal destruction with tuberculosis, but now autoimmune adrenalitis accounts for the majority of cases. Other causes include other infectious diseases (disseminated fungal infection), adrenal replacement by metastatic cancer or lymphoma, adrenal hemorrhage or infarction, or drugs that impair the synthesis of aldosterone (e.g. ketoconazole) [83].

Patients with chronic primary adrenal insufficiency may present with chronic malaise, fatigue, generalized weakness, anorexia, and weight loss. In most patients, the blood pressure is low and postural symptoms of dizziness and syncope are common. Salt craving is a distinctive feature in certain patients. Some patients may present with acute adrenal crisis and shock. Hyperpigmentation is evident in nearly all patients. Hyperkalemia is usually of moderate degree unless a si-

gnificant degree of intravascular volume depletion that diminishes the flow rate in CCD is also present. Other abnormal laboratory findings include hyponatremia, hyperchloremic metabolic acidosis, hypoglycemia, and eosinophilia.

– *Diagnosis requirement:* Once Addison's disease is suspected, the diagnosis is established by findings of low plasma aldosterone and cortisol levels, high PRA, and a blunted cortisol response to the administration of ACTH.
– *Molecular basis:* None
– *Therapy:* Adrenal crisis is a life-threatening emergency that requires immediate treatment to restore intravascular volume with the administration of saline and to correct the cortisol deficiency with the immediate administration of dexamethasone or hydrocortisone.

Patients with chronic adrenal insufficiency should receive replacement with both a glucocorticoid and a mineralocorticoid. For the former, 25 mg of hydrocortisone (15 mg in the morning and 10 in the afternoon) is usually given. For mineralocorticoid replacement, fludrocortisone in a single dose of 50 – 200μg is usually used. Dose adjustments are made based on patients' symptoms, ECF volume status, blood pressure measurements, and plasma $[K^+]$.

Pseudohypoaldosteronism Type I

– *Pathophysiology:* The underlying pathophysiology of this disorder is a "closed" ENaC in the CCD.
– *Clinical picture:* Patients with this rare inherited disorder usually present in the neonatal period with severe ECF volume contraction and renal salt wasting, hyperkalemia, metabolic acidosis, failure to thrive, and weight loss.
– *Diagnosis requirement:* Despite the clinical evidence of low actions of aldosterone, these patients fail to respond to exogenous mineralocorticoids. Furthermore, their plasma aldosterone levels and PRA are markedly elevated.
– *Molecular basis:* Mutations in the α or β subunits of ENaC that result in diminished ENaC activity have been identified [84]. This results in an autosomal recessive form of the disease with manifestations persisting into adult life. Other forms of the disease are autosomal dominant or sporadic ones and these may remit with age. They are believed to result from mutations in the mineralocorticoid receptor gene [85].
– *Therapy:* Treatment includes supplementation with NaCl and the use of cation-exchange resin to control the hyperkalemia. Dialysis may be required for treatment of life-threatening hyperkalemia. An interesting feature is that some of the affected children may grow out of the disease.

Syndrome of Hyporeninemic Hypoaldosteronism

– *Pathophysiology:* Patients with this syndrome represent a heterogeneous group with regard to the pathophysiology of their disorder. One group may have destruction of, or a biosynthetic defect in, the juxtaglomerular apparatus that leads to hyporeninemia, hypoaldosteronism, and hyperkalemia due to less luminal negative voltage in the CCD because of a relatively slower reabsorption of Na^+ in the CCD. In another group of patients, however, the pathophysiology seems to

be compatible with a Cl^--shunt disorder in the CCD [86]. This leads to expansion of the ECF volume and hence the hyporeninemia and hypoaldosteronism [26, 35, 87]. This relatively faster reabsorption of Cl^- in CCD causes the voltage across the CCD to be less electronegative and hence the low $[K^+]$ in the lumen of the CCD.

– *Clinical picture:* This syndrome is most commonly seen in patients with diabetic nephropathy but also has been associated with many other renal diseases. The clinical findings differ, based on the pathophysiology of the disorder. In the first group of patients one would expect to find renal salt wasting with a low ECF volume and inability to conserve Na^+ and Cl^- maximally in response to the stimulus of a contracted ECF volume. On the other hand, in the group of patients with a Cl^--shunt disorder, the ECF volume should be normal or expanded. Hypertension is commonly seen, and these patients should be able to produce a urine that is virtually free of Na^+ and Cl^- in response to contraction of their ECF volume.
– *Diagnosis requirement:* Both groups of patients have hyperkalemia with low PRA and plasma aldosterone levels that are low relative to the stimulus of hyperkalemia. The group with hyporeninemic hypoaldosteronism and a relatively slower reabsorption of Na^+ should respond to the administration of exogenous mineralocorticoids with a significant rise in their TTKG. On the other hand, patients with hyporeninemic hypoaldosteronism due to a Cl^--shunt disorder do not have an appreciable rise in their TTKG with the administration of exogenous mineralocorticoids, but their TTKG may rise significantly with the induction of bicarbonaturia (e.g. the administration of acetazolamide) [34].
– *Molecular Basis:* None.
– *Therapy:* Obviously the use of exogenous mineralocorticoids is of no benefit to the group of patients with a Cl^--shunt type of disorder. It may even aggravate their hypertension. In this group of patients, the administration of a loop or thiazide diuretic should enhance the kaliuresis by increasing the rate of flow in the CCD. This may also cause the loss of the excess Na^+ and may thereby help control hypertension. Diuretic therapy poses a threat to patients with hyporeninemic hypoaldosteronism with a low ECF volume. The administration of 9 α-fludrocortisone to these patients results in both a kaliuresis and retention of Na^+.

Hypertension and Hyperkalemia

– *Pathophysiology:* These patients represent a heterogeneous group. In some, the pathophysiology seems to be of a Cl^--shunt disorder in CCD [87]; in others the defect may be one of closed ENaC in CCD [57]. In this latter group, the renal salt wasting and the resultant ECF volume contraction lead to activation of the renin-angiotensin-system and possibly the release of other vasoactive mediators that could lead to the development of hypertension in patients who may be unduly sensitive to the action of these vasoconstrictors.
– *Clinical picture:* In both groups of patients there is the association of hypertension and hyperkalemia. In the group with a possible Cl^--shunt, the ECF volume is expected to be normal or expanded. On the other hand, patients with a possible closed ENaC are expected to have a low ECF volume.

– *Diagnosis requirement:* In patients with hypertension and hyperkalemia due to a Cl^--shunt, the PRA is suppressed, and the plasma aldosterone level is inappropriately low for the presence of hyperkalemia. These patients are expected to be able to excrete virtually Na^+- and Cl^--free urine in response to the induction of ECF volume contraction. The group of patients with hypertension and hyperkalemia due possibly to a relatively closed ENaC in the CCD are expected to have high PRA and high plasma aldosterone levels. Despite the presence of contracted ECF volume, these patients have renal salt wasting.
– *Molecular basis:* Genetic and molecular studies are needed in patients with hypertension, hyperkalemia, and possible closed ENaC to determine if these patients do indeed have inactivating mutations in ENaC.
– *Therapy:* Loop or thiazide diuretics are helpful in patients with hypertension and hyperkalemia due to a Cl^--shunt disorder. These agents, however, are likely to worsen the renal salt wasting and hypertension in patients with a relatively slower ENaC. Control of hypertension in these patients may be helped with salt supplementation.

Cyclosporin-induced Hyperkalemia

– *Pathophysiology:* Hyperkalemia develops in some patients receiving cyclosporin, as for instance, following organ transplantation. The pathophysiology of hyperkalemia in these patients resembles a Cl^--shunt disorder in the CCD [36].
– *Clinical picture:* These patients usually have hypertension in association with hyperkalemia. The PRA is suppressed, and the plasma aldosterone level is low relative to the stimulus of hyperkalemia.
– *Diagnosis requirement:* The administration of exogenous mineralocorticoids does not cause a rise in TTKG in these patients. A significant increase in the TTKG is observed following the induction of bicarbonaturia.
– *Molecular basis:* None.
– *Therapy:* Kaliuresis could be enhanced with the administration of a loop or thiazide diuretic to increase flow in CCD in these patients. Inducing bicarbonaturia with the use of acetazolamide could also be considered, but supplementation with bicarbonate may be required.

Trimethoprim-induced Hyperkalemia

– *Pathophysiology:* The cationic form of trimethoprim and pentamidine can cause hyperkalemia by blocking the ENaC in the CCD [31, 89, 90, 91].
– *Clinical picture:* Although first reported in patients with AIDS who received high doses of trimethoprim for the treatment of *Pneumocystis carinii* pneumonia [91], a rise in plasma [K^+] may occur in patients even when these agents are used in conventional doses [92]. Patients with AIDS may also have other conditions that make them prone to the development of a more severe degree of hyperkalemia: shift of K^+ from cells, decreased K^+ excretion because of a low flow in the CCD due to a low rate of osmoles (urea) excretion [25, 31].
– *Diagnosis requirement:* There is a history of intake of these drugs. Because these agents induce hyperkalemia by blocking the ENaC in the CCD, these patients also

have renal salt wasting with elevated PRA and plasma aldosterone levels.

– *Therapy:* Because only the protonated form of these drugs block ENaC, increasing the urine pH should cause less of the trimethoprim to be in its cationic form, and its antikaliuretic effect should be minimized [31]. Inducing bicarbonaturia with acetazolamide is a rational therapeutic option in patients with hyperkalemia in whom continuation of these drugs is necessary. However, enough alkali would need to be given to avoid the development of metabolic acidosis. The use of a loop diuretic may also help by lowering the concentration of these drugs in the urine. Enough NaCl administration will be required to maintain the ECF volume.

Hyperkalemic Periodic Paralysis (HYPP)

– *Pathophysiology:* The defect in this disorder seems to be in the regulation of a specific population of Na^+ channels (tetrodotoxin-sensitive) in the cell membrane in skeletal muscle. When the muscle is stimulated to contract, Na^+ influx depolarizes the cell. As the RMP approaches –50 mV, normal Na^+ channels close. In patients with HYPP, these defective Na^+ channels fail to close, causing the cells to have less negative RMP. Depending on the absolute voltage, lesser changes may result in myotonic seizures, while larger changes can cause paralysis.

– *Clinical picture:* This syndrome has an autosomal dominant inheritance. Symptoms of weakness and ultimately paralysis in association with hyperkalemia usually follow bouts of exercise.

– *Diagnosis requirement:* The diagnosis hinges on finding a characteristic clinical picture and is confirmed later by molecular studies.

– *Molecular basis:* This disorder is the result of a mutation in the alpha subunit of the skeletal muscle Na^+ channel gene [80, 81]. This leads to failure to completely close these voltage-gated Na^+ channels in skeletal muscle cells when the $[K^+]$ in the ECF is raised, and hence the electrical inexcitability of the skeletal muscle.

– *Therapy:* Treatment is directed at measures to avoid hyperkalemia. Acetozolamide seems to be effective, though its mechanism of action is not clear.

Therapy of Hyperkalemia When There is No Medical Emergency

It is important to recognize that lowering the plasma $[K^+]$ from 7 to 6 mM requires much less K^+ loss than what is needed to lower the plasma $[K^+]$ from 6 to 5 mM. Therefore, creating a small K^+ loss can be very important in severe hyperkalemia.

– *Diuretics and/or mineralocorticoids:* If K^+ excretion is low because of a low urine volume with a high $[K^+]$, a loop diuretic may induce kaliuresis by increasing the flow rate in the CCD (Figure 3). Unwanted ECF volume contraction can be avoided by replacing the NaCl lost in the urine. NaCl should be given at the same tonicity as the urine to avoid a dysnatremia. If the urine $[K^+]$ is unduly low, giving a mineralocorticoid (100 μg 9α-fludrocortisone) and inducing bicarbonaturia with the carbonic anhydrase inhibitor, acetazolamide may cause substantial kaliuresis (HCO_3^- lost in the urine may need to be replaced).

– *Cation-exchange resins:* The cation exchange resin that is most often used is Na^+ polystyrene sulfonate (Kayexalate). The resin can be given either orally or as a retention enema. It has the capacity to bind 3.5 mmol K^+/g of resin, but the actual amount bound in vivo is closer to 1 mmol K^+/g [92]. When used orally, 20 g of the resin is usually given with 100 mL of 20% sorbitol solution to avoid constipation. This can be repeated every 4 – 6 hours as needed. When given as an enema, 50 g of the resin is usually mixed with 50 mL of a 70% sorbitol solution and 100 mL of tap water. This solution is retained in the colon for at least 30 – 60 min, preferably longer. With this, the negative balance for K^+ that is usually achieved is 25 – 50 mmol). Sorbitol-induced colonic necrosis is a reported complication of this therapy in postoperative patients, perhaps reflecting decreased colonic motility that may increase the duration of contact of hypertonic sorbitol with the colonic mucosa. A cleansing enema may be needed to prevent the colonic retention of the resin-sorbitol mixture.

Metabolic Alkalosis

The hallmarks of metabolic alkalosis are an elevated [HCO_3^-] and decreased [H^+] in plasma [16, 94, 95]. As such, it is customary to discuss the topic of metabolic alkalosis in the section on acid-base disorders in most textbooks. We have chosen to break away from this tradition and include the discussion of metabolic alkalosis in the section on K^+. The reason for that decision is to emphasize that in conceptual terms, metabolic alkalosis due to vomiting is not primarily an acid-base disorder, but rather a disorder resulting for the most part from a deficit of KCl. Although metabolic alkalosis is defined clinically by changes in the composition of the ECF, presence of a high [HCO_3^-] in plasma, however, it is a disorder in which there is usually intracellular acidosis and a deficit of K^+ [15, 17].

Pathophysiology of Metabolic Alkalosis

To understand the pathophysiology of metabolic alkalosis, one must examine the total body balance for critical ions, analyzing events in 3 major areas: the ECF, the ICF, and the urine.

Mass Balance Data

The simplest model of metabolic alkalosis in humans is that produced when the only initial change in mass balance is to remove HCl from the stomach. In the most often-quoted study of this type of metabolic alkalosis [16], normal human volunteers underwent this process for 4 – 5 days. All ions and water losses other than HCl were replaced during that period. After this, subjects were allowed to stabilize in a post-drainage period of 5 – 7 days, during which their deficits of Cl^- were not replaced (Figure 17). Examining the mass balance data reveals that during the HCl drainage period, there was a deficit of Cl^- but not of Na^+ or K^+, and only a very modest decline in ECF volume. During the post-drainage period, however, all subjects developed a prominent degree of K^+ depletion due to renal K^+ loss. While it is not clear from the data what anion was excreted with K^+ in the urine, it is obvious that the source of K^+ was the ICF, as

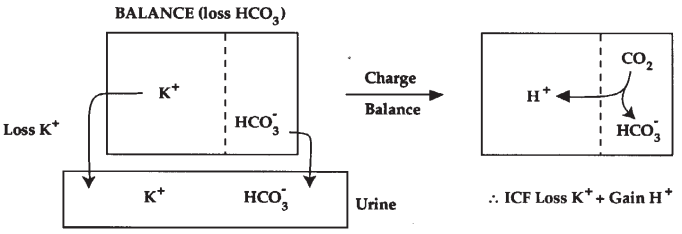

Figure 17. Stoichiometry when K^+ are excreted. When K^+ are excreted, there is a need to have a cation enter the ICF compartment (H^+ in this example) and an anion enter the urine with the K^+ for electroneutrality. The anions excreted are not Cl^-; they are HCO_3^- or their acid-base equivalents.

Table 6. Mass Balance for Na^+, K^+ and Cl^- in "Selective Depletion of HCl"'.
Data were selected from studies in the literature where there was selective loss of HCl (or swap of HCO_3- for Cl^-) together with a post-drainage period in humans [16], dog [105] or rat [17].

	Species		
Parameter	Human (mmol)	Dog (mmol)	Rat (μmol)
Na^+	-22	- 9	-535
K^+	-213	-118	-2931
Cl^-	-199	-110	-2533
ECF volume	-0.5 liters	—	-10 mL
–% change	-3	—	-12

there is not enough K^+ in the ECF to account for the magnitude of its negative balance. The striking feature is that on mass balance, there was near-equimolar losses of Cl^- and K^+ with little change in the mass balance for Na^+. Similar observations were made in experiments in animals. Mass balance data from human and animal experiments are summarized in Table 6.

H^+ Balance During KCl Depletion

Having established that the mass balance during this selective HCl loss (or so-called selective Cl^--depletion alkalosis, which is, of course, a misnomer because one must maintain charge balance) is one of equimolar loss of K^+ and Cl^-, then what is the mass balance for H^+ (Figure 17)? It is important to recognize that while there is equimolar loss of K^+ and Cl^-, the loss of these 2 ions did not occur in the same time frame or even by the same route. During the HCl drainage period, there was the loss of Cl^- with H^+, which resulted in a gain of HCO_3^- in the ECF (Figure 12). During the post-drainage period, K^+ were lost with anions other than Cl^-. If these anions were produced endogenously with H^+, their excretion in the urine with K^+ can be equated with a gain of H^+ in the body (Figure 17). Because the HCO_3^- content in the ECF did not decline when these H^+ were added to the body, they must have been retained in another compartment, the ICF. Because on mass balance data, there was an equimolar loss of K^+ and Cl^-, the HCO_3^- gain in the ECF was equiva-

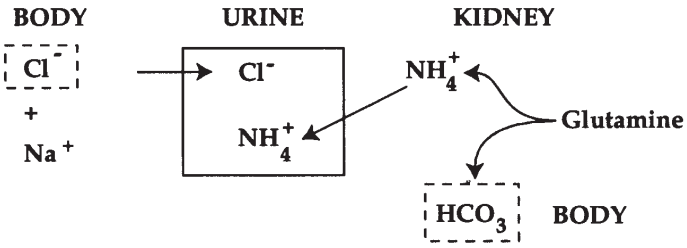

Figure 18. Stoichiometry when NH_4Cl is excreted. When NH_4Cl is excreted (solid box in center), there is a net loss of Cl^- together with the net gain of HCO_3^- in the ECF compartment (dashed boxes).

lent to the H^+ gain in the ICF, and the mass balance for H^+ was virtually nil.

To summarize, analysis of mass balance data during the simplest form of metabolic alkalosis, selective HCl loss, reveals a large KCl deficit. The mass balance for H^+ is largely nil with a HCO_3^- gain in the ECF and an equivalent gain of H^+ in the ICF. However, to recognize how the pathophysiology of metabolic alkalosis evolves, an analysis of events in 3 major areas, the ECF, the ICF and urine, is required.

Analysis of Events in Metabolic Alkalosis

Events in the ECF

With the constraints of electroneutrality, there are only 2 ways to add a specific anion to a compartment, either with a cation or an exchange for the loss of another anion.

In clinical disorders of metabolic alkalosis, the major way to add HCO_3^- to the ECF is to swap HCO_3^- for another anion in the ECF. The only anion present in sufficient quantities in the ECF is Cl^-. Because a loss of H^+ or NH_4^+ is equivalent to a gain of HCO_3^-, 2 organs are capable of inducing the swap of Cl^- for HCO_3^-: the stomach (HCl loss during vomiting or gastric drainage, Figure 12) and the kidney (excretion of NH_4Cl) (Figure 18).

Another way to add HCO_3^- to the ECF and yet maintain electroneutrality is the administration of HCO_3^- (or an anion that could be metabolized into HCO_3^-, e.g. citrate or acetate) along with a cation (Na^+). The normal diet supplies a load of alkali that is normally removed by excreting a family of organic anions [96]. With hypokalemia, the excretion of anions like citrate declines [97], and this will yield a net load of alkali to the body.

Renal Events

The early work of Pitts and coworkers has demonstrated a maximal tubular excretion (Tm) for HCO_3^- reabsorption by the kidney [98]. However, these experiments were done with the infusion of $NaHCO_3^-$ that also caused expansion of the ECF volume. In fact, in the absence of ECF volume expansion, the capacity of the proximal tubule for reabsorption of HCO_3^- is large, with no threshold for HCO_3^- reabsorption even at plasma [HCO_3^-] of close to 50 mM [99, 100, 101] (see chapter I-3 on *Acid-base Balance* for more discussion).

Two major factors seem to enhance the activity of the Na^+/H^+ exchanger (NHE-3) in the proximal tubule: Ang II [102] and intracellular acidosis. Ang II is released in response to low effective circulating volume. As the plasma [HCO_3^-] rises initially not all filtered HCO_3^- is reabsorbed. To the extent that some HCO_3^- is lost with Na^+ in the urine, a degree of contraction of the ECF volume occurs. With regard to the fall in intracellular pH, both hypokalemia and a rise in pCO_2 raise the [H^+]

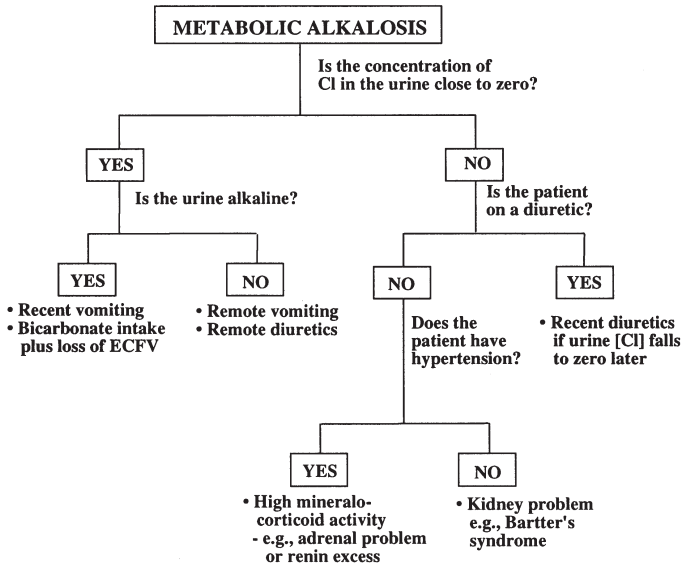

Figure 19. Diagnostic flow chart for metabolic alkalosis. For details, see text. Final diagnoses are shown in the boxes at the bottom of each limb of the flow chart. Reproduced with permission [104].

in the ICF and hence the activity of NHE-3 in the PCT. These renal mechanisms lead to HCO_3^- retention and protect against bicarbonaturia with the associated loss of Na^+ (loss of ECF volume) and K^+ (worsening hypokalemia). Moreover, the loss of HCO_3^- must be prevented as the body does not have a total HCO_3^- surplus.

Events in the ICF

As discussed previously, mass balance data reveal a large deficit of K^+. The source of this K^+ is from the ICF, and its loss in the urine occurs with an anion other than Cl^-. The loss of K^+ with an endogenous anion is equivalent to the gain of H^+ (see Figure 17). To provide mass balance and electroneutrality for the ECF and ICF, H^+ and Na^+ enter the ICF as K^+ exit. Therefore, there is both depletion of K^+ and intracellular acidosis.

To summarize, the pathophysiology of the so-called Cl^- depletion metabolic alkalosis has the following features: a higher content and concentration of HCO_3^- in ECF, an enhanced reabsorption of HCO_3^- by the kidney, and K^+ depletion with intracellular acidosis.

Clinical Aspects of Metabolic Alkalosis

A list of the common causes of metabolic alkalosis is provided in Figure 19. Metabolic alkalosis is seen most often in patients who vomit on a chronic basis or those who are taking diuretics. Less commonly, causes include patients with disorders of primary excess of mineralocorticoid actions. The most helpful aspects in the differential diagnosis on presentation are the history, an assessment of the ECF volume, the measurements of the plasma creatinine concentration, and an analysis of electrolyte excretion in a random urine.

History

Often, the diagnosis of metabolic alkalosis is straightforward. However, a number of patients are not willing to admit to self-induced vomiting or the abuse of diuretics. Therefore, the history cannot be relied upon entirely, and one must often resort to a series of laboratory tests to establish the diagnosis (Table 1).

Assessment of the ECF Volume

The major causes of metabolic alkalosis, vomiting or diuretic abuse, are usually accompanied by a significant degree of ECF volume contraction. On the one hand, patients with metabolic alkalosis due to primary excess of mineralocorticoid actions have a normal or somewhat expanded ECF volume. Hypertension is also a common finding in these patients.

Urine Electrolytes

A single spot urine, or perhaps several spot urine samples, can unravel the pathophysiology of metabolic alkalosis (Table 1). It must be stressed at the outset that there are no normal values for urine electrolytes, just expected values in a given clinical setting.

In patients with metabolic alkalosis, ECF volume contraction, and similar low excretions of Na^+, K^+ and Cl^- could represent the presence of remote vomiting or 'yesterday's diuretics', or the prior intake of nonreabsorbable anions. Some patients with metabolic alkalosis have a low rate of Cl^- excretion, yet the urine contains an abundant quantity of Na^+. The reason for the Na^+ excretion is the presence of an anion that was not reabsorbed. If the urine contains a large quantity of HCO_3^- (pH > 7), vomiting or nasogastric suction are the most likely diagnoses. A low urine pH suggests the intake of anions that are poorly reabsorbed by the kidneys.

Excretion of an abundant amount of Na^+ and Cl^- in the urine is expected in a patient with a normal ECF volume. In a patient with metabolic alkalosis and a contracted ECF volume, this pattern of electrolyte diuresis suggests a diagnosis of Bartter's or Gitelman's syndrome(s) or the recent use of diuretics.

Plasma Creatinine

Some patients with ECF volume contraction will have elevated values for plasma creatinine corrected for their body mass, especially if the degree of ECF volume contraction is marked. Previous values and the clinical setting make this interpretation relatively simple.

Patients with chronic renal failure (CFR) usually have a normal or expanded ECF volume and a markedly elevated level of creatinine in plasma. If a patient with renal failure ingests or is given alkali or organic anions, little HCO_3^- will be filtered and HCO_3^- will be retained.

Clinical Approach

An outline to a clinical approach to a patient with metabolic alkalosis is provided in Figure 19. The first step in the resolution of the basis of metabolic alkalosis is to rule out the presence of significant renal function impairment (GFR < 25% of normal). If renal failure exists, the specific cause of the metabolic alkalosis should be evident from the history.

If a very low GFR plus alkali input is not the cause of metabolic alkalosis, the ECF volume status is the next critical parameter to assess. The majority of patients have a contracted ECF volume and their urine [Cl^-] is very low (< 20 mM). The differential diagnosis in this group of patients with a contracted ECF volume is indicated in Figure 19.

Effect of Metabolic Alkalosis on Ventilation

The [H^+] is a major determinant of ventilation, and therefore one would expect metabolic alkalosis to have a depressant effect on ventilation. In fact, there is a linear relationship between the increasing plasma [HCO_3^-] and progressive increase in the partial pressure of carbon dioxide (pCO_2), with a slope of approximately 0.7, indicating that for every mM increase in plasma [HCO_3^-], a 0.7 mmHg increase in pCO_2 would be expected. Thus, when patients present with CO_2 retention and metabolic alkalosis, the metabolic alkalosis should be corrected before attributing the CO_2 retention to lung disease.

As hypoventilation develops, it is accompanied by hypoxia, which offsets the degree of respiratory suppression achieved. The reduction of tissue oxygen (O_2) delivery in metabolic alkalosis is further aggravated by the fact that the O_2 hemoglobin dissociation curve is shifted to the left by alkalemia, increasing the affinity of hemoglobin for O_2.

Patients with chronic lung diseases often take diuretics to cope with their Na^+ retention and may develop metabolic alkalosis. The mixed acid-base disturbance may return their plasma [H^+] to the normal range. This removes the acidemic drive to ventilate and may worsen the clinical condition [103].

Treatment of Patients with Metabolic Alkalosis

Group with a Low ECF or Effective Circulating Volume

It goes without saying that patients with ECF volume contraction require Na^+ and Cl^- replacement. When their ECF volume is restored, the [HCO_3^-] will fall, owing to dilution. Eventually there will be some bicarbonaturia. Moreover, the [HCO_3^-] in the ECF can fall to the normal range when a large excess of NaCl is given (the ECF volume is expanded by 4 – 5 L), even if the K^+ deficits are not completely restored [94]. Up to this point the large K^+ deficit in cells and the intracellular acidosis have been ignored. Therefore, NaCl administration is only partial therapy in patients with metabolic alkalosis who have ECF volume contraction, as it does not address the accompanying intracellular acidosis and K^+-deficit. In fact, some patients with metabolic alkalosis have only a marginal depletion in their ECF volume. Clearly in this case, NaCl should not be the linchpin of therapy. To treat the ICF acidosis and K^+ depletion, obviously K^+ must be given with an anion that permits retention of this cation in the ICF. This means KCl in most cases because as K^+ enters the ICF, Na^+ and H^+ exit for the most part. The H^+ titrates the excess HCO_3^- in the ECF and the extra NaCl is excreted.

In patients in whom the metabolic alkalosis is due to a reduction in effective circulating volume with ECF volume expansion (e.g. congestive heart failure (CHF) on diuretics), the metabolic alkalosis requires therapy with KCl, and additional Na^+ should *not* be given (as K^+ enters the ICF, Na^+ leaves, adding some Na^+ to the ECF). A loop diuretic will be needed to excrete the net gain of NaCl in the ECF compartment.

If the patient has been abusing diuretics or inducing vomiting, therapy of the underlying psychopathology proves to be the greater problem.

If the patient is ventilated and has a fixed alveolar ventilation, the pCO_2 may rise with H^+ administration. Therefore, in these patients, treatment must be very slow.

High or Normal ECF Volume Group

Therapy is generally more difficult in patients with ECF volume expansion. If they have renal failure and are very alkalemic ($[H^+]$ < 20 nM, pH > 7.70), they should receive some H^+ in the form of HCl or NH_4Cl. If these patients are dialyzed, the bath should have the $[HCO_3^-]$ reduced so as to ameliorate rather than contribute to the alkalemia.

If the patient has hyperadrenalism, agents blocking the reabsorption of Na^+ by the ENaC in the CCD (amiloride) or mineralocorticoid antagonists have an important role in the therapy. Aggressive K^+ replacement in conjunction with amiloride or spironolactone must be used with caution, so as to avoid the development of a serious degree of hyperkalemia [60, 61]. In the acute setting, it is safest to order only one day of K^+ therapy at a time, checking the serum $[K^+]$ each day before ordering that day's therapy.

Patients with Mg^{2+} deficiency should have their deficiency corrected, but it is important to follow up on the effectiveness of the therapy, since patients with hyperaldosteronism also have Mg^{2+} deficiency.

At times, one would like to alleviate the alkalemia quickly (e.g. weaning from a ventilator). Acetazolamide is sometimes used in such a setting, but the large load of $NaHCO_3$ delivered to the collecting duct can promote a substantial additional urinary K^+ loss. For this reason, we prefer an IV HCl preparation in such patients. With IV HCl, one also has better control over the degree of fall in $[HCO_3^-]$ than with acetazolamide.

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Disorders of Acid-base Balance

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Overview of Hydrogen Ions

Hydrogen ions (H^+) play a central role in cellular physiology [1, 2]. Their most important function is in the regeneration of adenosine triphosphate (ATP) that permits cells to perform biological work. To regenerate ATP, H^+ are first actively pumped out of mitochondria using energy derived from a redox pump; this creates an electrochemical driving force for H^+ to enter mitochondria. This proton motive force across the inner mitochondrial membrane is largely due to voltage (inside negative) and also to a pH difference (inside alkaline). When H^+ diffuse into the mitochondrial compartment, the entry system has two components, a special H^+-ATP synthetase that is linked to a system to convert ADP plus inorganic phosphate to ATP. This system of linking H^+ transport and ATP turnover is a fundamental one in acid-base homeostasis. For example, the reverse of this reaction causes H^+ to be transported out of cells of the collecting duct with the driving force being the hydrolysis of ATP – the H^+ pump is now an H^+-ATPase using energy trapped in ATP to move H^+ against its electrochemical gradient [3].

The H^+ concentration in all body compartments is maintained at a very low level because H^+ bind very avidly to histidine residues in proteins. Binding of H^+ to proteins changes their charge (more positive) – this might alter their configuration, and possibly their function [4]. Since most proteins are enzymes, transporters, contractile elements, and structural compounds, a change in their function could pose a major threat to survival. Notwithstanding, not all H^+ binding to proteins results in a diminished function; for example, H^+ binding to hemoglobin promotes the release of O_2 at the tissue level and the converse applies in the alveoli of the lung [5].

Two quantitative aspects illustrate this delicate homeostasis for H^+. First, the concentration of H^+ in plasma is exceedingly tiny as compared to the concentrations of ions like bicarbonate (HCO_3^-) (P_{HCO3}), sodium (Na^+) (P_{Na}), potassium (K^+) (P_K), or chloride (Cl^-) (P_{Cl}). Moreover, the concentration of H^+ is maintained within a very narrow range in the extracellular fluid (ECF) (40 2 nM) or in cells (close to 80 nM in many cell types) [6]. This is even more impressive because an enormous number of H^+ are produced and removed by metabolism each day [7]. In more detail, acids are obligatory intermediates of carbohydrate, fat, and protein metabolism. For example, since adults typically consume (and oxidize) 1,500 mmol of glucose per day, at least 3,000 mmol or 3,000,000,000 nmol of H^+ are produced (as pyruvic and/or L-lactic acids) and removed daily. In an adult eating a typical Western diet, 70 mmol or 70,000,000 nmol of these H^+ are added to the body. This implies that there are very effective control mechanisms that minimize fluctuations in the concentration of H^+, thereby avoiding large changes in the net valence on body proteins.

Table 1. Major concepts in acid-base balance. For details, see text. Reproduced with permission [187].

Concept	Comment
1. Net H^+ production is revealed by finding new anions.	The rate of turnover of ATP sets an upper limit on the rate of ketoacid and L-lactic acid production and removal. Diminished metabolic removal of ketoacids is critical for ketoacid accumulation.
2. Buffering of H^+ is good if H^+ are removed by HCO_3^- and not proteins.	A low tissue PCO_2 is needed for the BBS. Tissue PCO_2 depends on the arterial PCO_2, CO_2 production and blood flow rates.
3. Kidneys add new HCO_3^- to the body by excreting NH_4^+.	NH_4^+ production is stimulated by a low PCT cell pH, and is limited by PCT ATP turnover and the presence of an alternate fuel.
4. Eliminate dietary alkali with endogenous H^+ production.	Alkali is eliminated by organic acid production and the excretion of organic anions in the urine as their Na^+ and K^+ salts.
5. Excrete urine at a pH of 6.0.	Arguably, this is the most important renal function in acid-base balance because a urine pH of 6 minimizes the risk of uric acid and $CaHPO_4$ stone formation.

BBS = Bicarbonate Buffer System.

Overview of Acid-base Balance

An analysis of acid-base balance must consider not only acid balance but also the balance for bases or alkali.

Acid-balance

There are 3 major components to consider in the physiology of acid balance (Figure 1). First, during the metabolism of certain dietary constituents, H^+ are produced. This production of H^+ is recognized by finding of the appearance of new anions (Table 1) [2, 7]. Second, H^+ are ultimately removed from the body largely because they react with HCO_3^-, forming CO_2 + water; the CO_2 so-formed is eliminated via the lungs. The net result of these reactions is a deficit of HCO_3^- in the body that is equal to the net H^+ load. Third, generate new HCO_3^- (without H^+) to replace that lost in titrating these H^+ [8]. This is accomplished by excreting ammonium ions (NH_4^+) in the urine.

Base-balance

The diet also provides alkaline salts [9]; the best example is the ingestion of fruits that contain K^+ citrate salts. Metabolism of these citrate anions occurs rapidly in the liver and

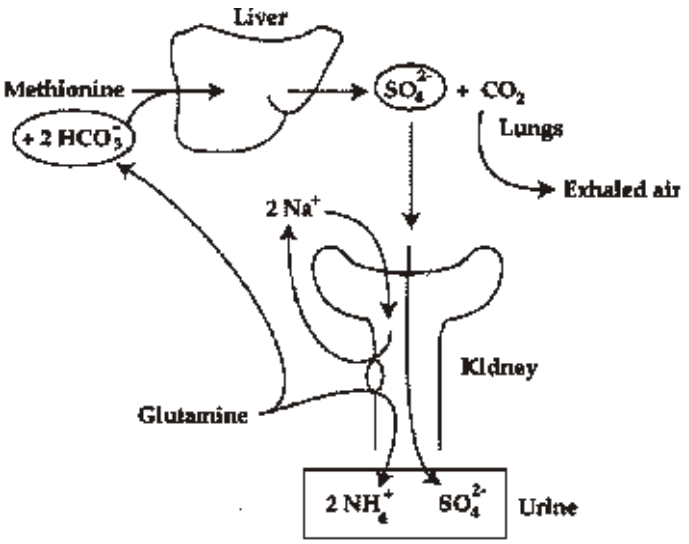

Figure 1. Acid balance. The portion of new H^+ produced in metabolism that requires renal actions for its elimination come from the oxidation of sulfur-containing amino acids depicted as methionine oxidation in the liver. This process removes HCO_3^- from the body and adds SO_4^{2-} anions. The kidney excretes these extra SO_4^{2-} anions while adding an equal quantity of HCO_3^- to the body. This is achieved as equivalent amounts of $NH_4^+ + SO_4^{2-}$ are excreted in the urine. Reproduced with permission [187].

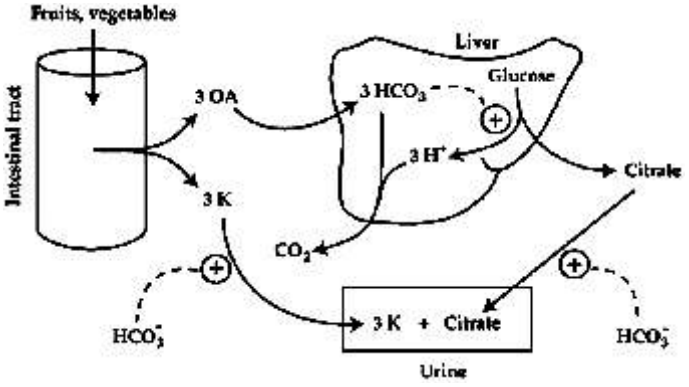

Figure 2. Disposal of an alkali load. The alkali load of the diet is derived from ingested K^+ salts of organic anions for the most part. This spectrum of organic anions is converted to HCO_3^- in the liver. Organic acids (citric acid in this example) are then produced by hepatocytes and its conjugate base (citrate anion) will be excreted in the urine as a K^+ salt. Reproduced with permission [187].

the net result in acid-base terms is the production of HCO_3^- [7]. Removal of this HCO_3^- load is achieved via production of new endogenous organic acids including citric acid [9]. The H^+ of these acids titrate HCO_3^- and base balance is maintained by excreting the conjugate base of these acids (e.g., $citrate^{3-}$) in the urine as their Na^+, K^+, and/or calcium (Ca^{2+}) salts [2, 9 – 12] (Figure 2). This disposal of alkali with the excretion of organic anions minimizes the risk for kidney stone formation. It avoids the excretion of HCO_3^- which, by alkalinizing the urine, could lead to calcium phosphate precipitation [13]. Further, in response to a load of alkali, renal reabsorption of citrate declines [14], citrate chelates Ca^{2+} in the urine and therapy reduces the risk of stone formation.

H^+ Production

CONCEPT 1: H^+ production is revealed by finding of new anions.

Metabolic analysis of net production of acids: A metabolic process can span more than one organ (Figure 3). In general, the starting

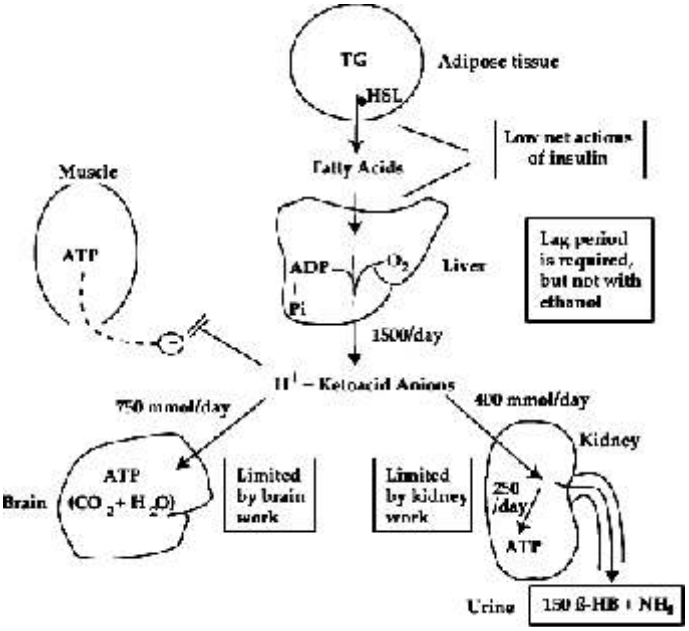

Figure 3. The metabolic process involved in ketoacid metabolism. The metabolic process of ketoacid metabolism begins with activation of hormone sensitive lipase (HSL) in adipose tissue. After a lack of insulin for several days, the production of ketoacids in the liver rises to about 1500 mmol/day. The main sites of removal of ketoacids are the brain (750 mmol/day) and the kidneys (400 mmol/day). Reproduced with permission [187].

points are dietary or stored fuels (glycogen or triglycerides) and the final products are ATP or storage forms of fuels [2]. From an acid-base perspective, one can determine if H^+ are produced or consumed in a metabolic process by a quantitative examination of the net charge or valence of its substrates and end products [7]. H^+ are formed if the net charge of the compounds produced is more anionic than that of substrates; the converse is also true. In this analysis, the net charge on adenine nucleotides (ADP, AMP, ATP) or NAD(P) does not need to be considered as the conversion of ATP to ADP to do biological work initiates the regeneration of ATP and NAD(P).

Acid balance is maintained if the new anions are metabolized to neutral end products, or if they are excreted in the urine along with H^+ or NH_4^+. On the other hand, there is a net gain of H^+ in the body if these anions are retained in the body or are excreted as their Na^+ or K^+ salts. Therefore every new anionic valence retained in the body or excreted with Na^+ or K^+, one new H^+ was added (Figure 4). Using the above analysis, the net addition of H^+ to the body can be classified into 2 categories:

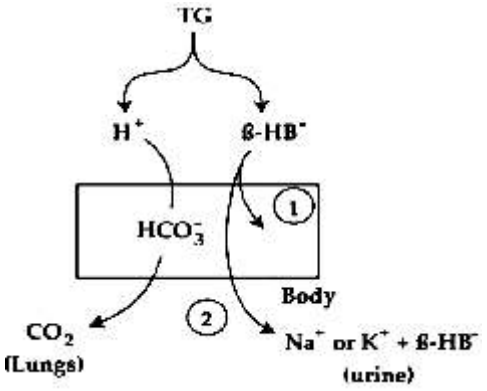

Figure 4. Metabolic analysis of net production of acids. The partial oxidation of storage triglyceride (TG) yields H^+ plus -hydroxybutyrate anions (--HB^-). The H^+ are titrated in the body by HCO_3^-, generating water and CO_2 – the latter is exhaled and the body has a deficit of HCO_3^- and a gain of -HB^-. If the -HB^- are retained in the body (point 1) or are excreted as Na^+ (or K^+) salts (point 2), there is a deficit of HCO_3^- that is equivalent to a net gain of H^+. Reproduced with permission [187].

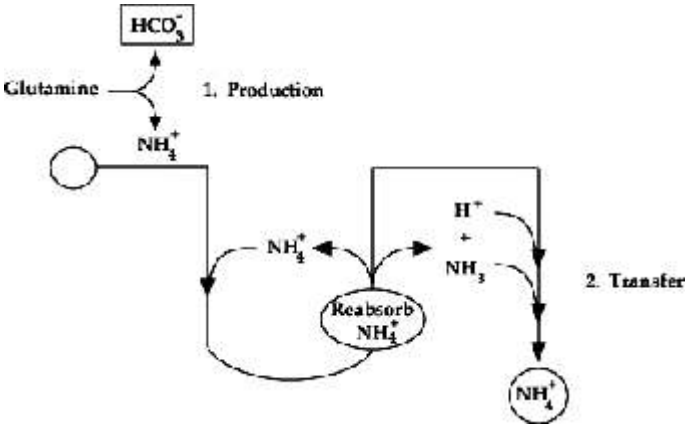

Figure 5. Physiology of NH_4^+ excretion. There are 2 major steps. First, NH_4^+ and HCO_3^- are produced when glutamine is metabolized in cells of the PCT. Second, NH_4^+ is transferred via the medullary interstitial compartment to the lumen of the MCD because of a high medullary interstitial concentration of NH_3 and NH_4^+.

– *H^+ production during normal metabolism:* In effect, this means the production of sulfuric acid (SO_4^{2-} anion + 2 H^+) from the oxidation of sulfur-containing amino acids and the production of phosphoric acid from the oxidation of monovalent phosphate diesters. These latter H^+ are removed when they are excreted bound to phosphate in the urine as $H_2PO_4^-$ (titratable acid excretion). On the other hand, H^+ that are produced with sulfate (SO_4^{2-}) anions during metabolism of sulfur-containing amino acids cannot be removed via metabolism or by excreting SO_4^{2-} in the urine because the affinity of SO_4^{2-} for H^+ is too low at typical urine pH values. In this case, maintenance of acid balance requires a mechanism for the generation of new HCO_3^- *without* adding H^+ to the body. This is accomplished by metabolizing a neutral amino acid, glutamine, to a cation (NH_4^+) and an organic anion (-ketoglutarate). This anion is metabolized in the kidney to a neutral end product (CO_2 and/or glucose), yielding new HCO_3^- that are added to the body. For a net gain of HCO_3^-, NH_4^+ must be made into an end product of metabolism by being excreted in the urine (Figure 5) [15].

– *H^+ production during incomplete or abnormal metabolism:* We cite 3 major examples here. First, the fastest rate of production of H^+ is from carbohydrate metabolism when the supply of oxygen is inadequate to meet demands. Now L-lactic acid is generated by anaerobic glycolysis (Table 2). Although metabolism of the L-lactate$^-$ anion to a neutral end product (e.g., glucose, glycogen or CO_2) removes H^+, this occurs at a much slower rate. Second, H^+ production occurs during fat metabolism if there is a relative lack of insulin. In this case, ketoacids (-hydroxybutyric acid and acetoacetic acid) are formed [16]. The degree of ketoacidosis depends on how quickly the brain and the kidneys remove these acids. Third, at times, compounds are ingested (usually alcohols or precursors of alcohols) that can be metabolized to anions at a much faster rate than these anions can be converted to neutral end products to remove these H^+.

Endogenous net production of acids, a physiological analysis: We can identify 2 major categories of endogenous acid production. One type of H^+ production requires renal net acid excretion to eliminate these H^+ (e.g.,

Table 2. Rates of production of H^+ and its removal. The rate of L-lactic acid production listed in this table is that occur during anaerobic metabolism, assuming an O_2 consumption rate of 12 mmol/min and that the rate of turnover of ATP is unchanged. This rate is much greater than in all other causes of net H^+ addition. H^+ removal by metabolism of L-lactate anions is depicted for gluconeogenesis and oxidation in the liver and kidneys.

	Rate (mmol/min)
Production of H^+	
– L-lactic acid during anoxia	72
– ketoacids during a lack of insulin	(up to) 1.5
– methanol/ethylene glycol	(up to) 1.0
Removal of H^+	
– *renal generation of new HCO_3^-*	
– normal	0.03
– chronic acidosis	0.15
– *metabolism (maximum in vivo rates in mmol/min)*	
– L-lactic acid	4 – 8
– ketoacids in brain and kidneys	1.0

monovalent diester phosphates and sulfur-containing amino acids described above). H^+ produced in metabolism of sulfur-containing amino acids are eliminated by the excretion of an equivalent amount of NH_4^+ in the urine. The second type of dietary-driven H^+ production is part of the physiological response to eliminate the dietary alkali (part of base balance, Figure 2, [9, 11]). This process yields H^+ plus organic anions – H^+ titrate HCO_3^-, while the organic anions are made into end products of metabolism by being excreted in the urine as their Na^+ and/or K^+ salts. Hence although both types represent endogenous H^+ production, they have very different functions.

Basis for metabolic acidosis: There are 3 ways to raise the concentration of H^+ in the body – the addition of acids that yield H^+ (one form of metabolic acidosis), failure to eliminate CO_2 normally (called respiratory acidosis), and failure to add new HCO_3^- to the body by excreting enough NH_4^+ (another form of metabolic acidosis). In yet another condition, H^+ may redistribute from the ECF to the intracellular fluid (ICF) compartments without requiring an overall change in the total number of H^+ in the body. An example of such a shift of H^+ into cells occurs in patients with a large deficit of K^+. In this case one develops an intracellular gain of H^+ together with a gain of HCO_3^- in the ECF compartment [17, 18]; from the perspective of the ECF, this is called metabolic alkalosis, but from the perspective of the ICF compartment, it would be called metabolic acidosis and a deficit of K^+ (see Chapter on K^+ where metabolic alkalosis is considered in more detail).

Tools to HelpIdentify Net Production of Acids

Metabolic acidosis that is due to an overproduction of acids can be recognized by finding the "footprints" of the added acids,

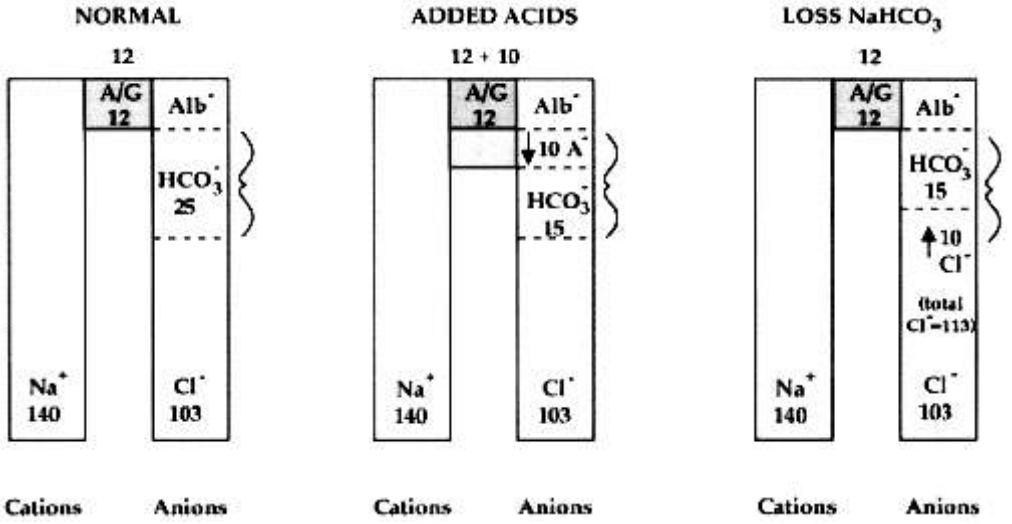

Figure 6. Plasma anion gap. The anion gap is a calculation for "diagnostic convenience"; it reveals the "footprints" of added acids. One measures only the major cation Na^+ and subtracts the major anions Cl^- and HCO_3^-. The usual value is 12 mEq/l (140 – 103 – 25); the anion that is not measured as such is primarily albumin. When acids are added and their anions are retained in the ECF compartment, the P_{HCO3} falls and the extra anions are revealed by the larger value for the plasma anion gap. When $NaHCO_3$ is lost, the P_{HCO3} falls and there are no extra anions; rather, the P_{Cl} rises.

their conjugate bases (or new anions) in the body (Figure 6) or in excreted fluids (usually the urine). At times one can gain a helpful hint about the nature of the added acids from examining the renal handling of their anions.

New anions in the body: New anions in the body are detected by calculating the anion gap in plasma (Figure 6). The concentration of unmeasured anions in plasma (the plasma anion gap) is the difference between the concentrations of the measured cation (Na^+) and the measured anions (Cl^- and HCO_3^-) in plasma (Equation 1). K^+ is not commonly included in this anion gap calculation because its concentration is low relative to that of Na^+. The usual normal range for the plasma anion gap is 12 2 mEq/l and this reflects for the most part, the net anionic valence of albumin in plasma. In some laboratories, this value may be closer to 6 or 8 mEq/l due to higher reported values for Cl^- because of different analytical techniques for measurement of Cl^-.

$$\text{Plasma anion gap} = P_{Na} - (P_{Cl} + P_{HCO3}) = 12 \quad 2\,\text{mEq/l} \qquad (1)$$

If the value for the plasma anion gap is higher than expected for the anionic valence on albumin, this suggests that acids have accumulated (Figure 6, middle panel). There are, however, some potential pitfalls to consider when evaluating the plasma anion gap. The net anionic charge on albumin accounts for most of this "gap". At a plasma pH of 7.4 and a concentration of albumin is 40 g/l or 4 g/dl, its valence is close to 12 mEq/l (when the valence on K^+ is ignored) [19]. Therefore a low concentration of albumin in plasma will cause the "baseline" value for the anion gap in plasma to be lower; as a clinical short cut, for

every 10 g/l decline in albumin concentration, one should anticipate a 3 – 4 mEq/l fall in the "baseline" value for the plasma anion gap.

Another cause for a low anion gap in plasma is the presence of unusual cations in plasma such as myeloma proteins. Although hypercalcemia or hypermagnesemia will in theory lower the value for the plasma anion gap, the change in their concentrations is rarely high enough to make a significant change in the plasma anion gap; the same is true for other cations such as lithium. A low plasma anion gap can be due to overestimation of Cl^- (e.g., bromism).

Renal handling of new anions: The renal handling of anions produced in association with H^+ has an important effect on the magnitude of the rise in the plasma anion gap as compared to the decrease in the P_{HCO3} [20]. One can utilize the renal handling of these anions to help recognize which acid was produced. For example, if the new anions are retained in plasma, this implies that there was little excretion of these anions in the urine. For the most part, this means either a low rate of filtration (low GFR), protein binding, and/or avid reabsorption of these new anions by the kidney (L-lactate anions, ketoacid anions, and to a lesser extent, D-lactate anions). On the other hand, metabolic acidosis due to a high rate of production of acids can be associated with a near-normal anion gap in plasma if the accompanying anion is largely excreted in the urine; an example is the production of hippuric acid and excretion of the anion, hippurate as its Na^+ or K^+ salt (e.g., in glue sniffers [21]).

Plasma osmolal gap: This tool is used primarily to detect uncharged, low molecular weight precursors of acids. In practice, the calculation of the plasma osmolal gap is used to detect toxic alcohols (methanol and ethylene glycol). The plasma osmolal gap is defined as the difference between the measured and the calculated plasma osmolality (P_{Osm}). The calculated P_{Osm} is the sum of twice the plasma P_{Na} plus the concentration of glucose (P_{Glu}) and of urea (P_{Urea}) in plasma, all in mM terms (Equation 2). To convert to mM terms, divide the BUN in mg/dl by 2.8 and the P_{Glu} in mg/dl by 18.

$$\text{Plasma osmolal gap} = \text{Measured } P_{Osm} - ((2 \times P_{Na}) + P_{Urea} + P_{Glu}) \quad (2)$$

To use this calculation, one must presume that there is no error in measurement of P_{Na} (e.g., due to hyperlipidemia). Ethanol will also be detected by the calculation of the plasma osmolal gap. Therefore one should not think that methanol or ethylene glycol is absent simply because there is a history of consumption of ethanol. At times, compounds such as mannitol, or very high concentrations of ions such as Mg^{2+} may cause a high value for the plasma osmolal gap. When there is methanol or ethylene glycol toxicity, the value for the plasma osmolal gap is usually considerably greater than 25 mOsm/kg H_2O.

Buffering of H^+

CONCEPT 2: In physiological buffering, H^+ are to be removed by the bicarbonate buffer system and not by proteins.

In the traditional view, the role of buffering is to minimize the change in the concentration of H^+ when an acid or alkali is added to a solution. From a physiological perspective, however, the main role of buffering is to force H^+ to bind to HCO_3^- rather than to proteins [4]. Binding of H^+ to intracellular proteins could be detrimental to cellular function because this changes the charge on these proteins which could alter their tertiary structure and may thereby affect their function. Therefore, while it is customary to rely on measurements

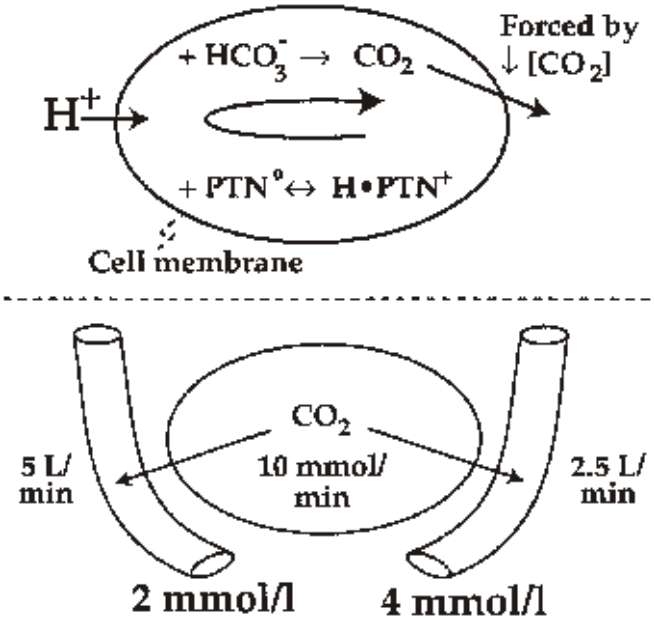

Figure 7. Role of the tissue PCO_2 in the selection of ICF buffers. As shown in the top portion of the figure, when the tissue PCO_2 falls, the H^+ concentration in cells will decrease and these H^+ will be removed by HCO_3^-. This will reduce the quantity of H^+ bound to intracellular proteins ($H\bullet PTN^+$). As shown in the bottom portion of the figure, there will be a rise in the cell and venous PCO_2 when the blood flow rate is slower (2.5 vs 5 l/min), as may be the case in a patient with a contracted ECF volume. This higher cell PCO_2 forces H^+ to bind to proteins. The converse occurs when the ECF volume is re-expanded.

in plasma (pH, PCO_2, P_{HCO3}^-) to assess the acid-base disturbance, it is also important to recognize that events in the ECF, and especially in arterial blood, may not reflect the acid-base status in the ICF compartment.

Several factors determine the degree of binding of H^+ to intracellular proteins (Figure 7). The first step for buffering of H^+ in cells is that they must cross cell membranes. Buffering by intracellular HCO_3^- can only occur if the tissue PCO_2 falls (Equation 3).

$$H^+ + HCO_3^- \quad H_2CO_3 \quad H_2O + CO_2 \qquad (3)$$

Distribution of H^+ Between the ECF and ICF

This issue will be considered in some detail because it also provides the basis to understand why hyperkalemia develops in patients with certain types of metabolic acidosis [22]. To shift K^+ out of cells, the mechanism of entry of H^+ into cells should cause a less negative voltage in cells. H^+ move across cell membranes by passive entry of electroneutral free acids or by carrier-mediated transporters for monocarboxylate acids. With regard to the former, diffusion must be very slow because the concentration of free acids with pK values in the 2 – 4 range are very low at the pH of body fluids. Hence specific transport systems that permit H^+ to cross cell membranes are the most important pathways to understand (Figure 8).

H^+ do not appear to enter cells by ion channels because if H^+ or HCO_3^- ion channels were present and open in cell membranes, the ratio of the concentration of H^+ in the ICF and ECF compartments would be similar to that of K^+. Therefore the concentration of H^+ in the ICF compartment would be 30 – 40 times higher than that in the ECF compartment – i.e., the pH of the ICF compartment would be close to 1.5 pH units lower than the ECF while measured values are close to 0.3 pH unit [6]. Three pathways are available for electroneutral H^+ movement.

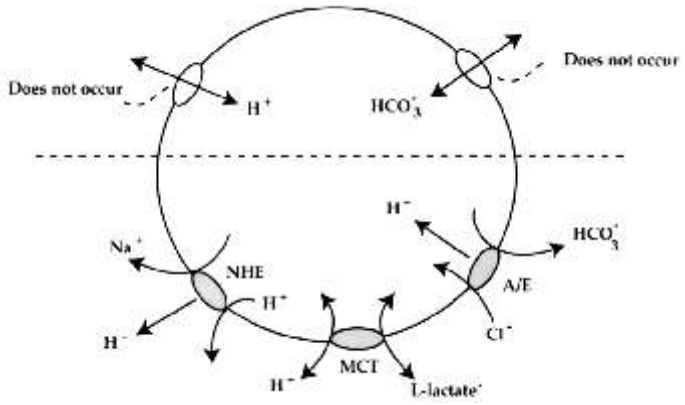

Figure 8. Pathways for net H^+ transport across cell membranes. The circle represents a cell. Given the large net ICF negative voltage across cell membranes and the 2-fold H^+ concentration difference, H^+ or HCO_3^- ion channels could not be in an open configuration (open ovals above the dashed line). Rather, there are 3 possible transport systems, as shown by the shaded ovals, which could lead to the net transport of H^+. Abbreviations: NHE = Na^+/H^+ exchanger; MCT = monocarboxylic acid transporter; AE = Cl^-/HCO_3^- anion exchanger.

(i) The monocarboxylic acid transporter (MCT): The MCT catalyzes, for example, the cotransport of L-lactate$^-$ or -HB$^-$ anions plus H^+ across cell membranes [23]. Because flux through this cotransporter is electroneutral, it does not cause a change in the resting membrane potential. Therefore this form of transport of H^+ does not lead directly to a shift of K^+ across cell membranes.

(ii) The Na^+/H^+ exchanger (NHE): A simple examination of existing concentrations of Na^+ and H^+ in the ECF and ICF compartments indicates that the NHE must be largely inactive in vivo because it is appreciably displaced from its electrochemical equilibrium (Na^+ concentration in the ECF compartment is higher (140 vs ~ 14 mM) and lower H^+ concentration is lower (40 vs 80 nM) in the ECF compartment). When NHE does become active, the only direction for net movement of H^+ is from the ICF to the ECF compartment [24]. Hence NHE is *not* directly involved in buffering of an ECF H^+ load.

(iii) The chloride (Cl^-)/HCO_3^- anion exchanger (AE): This AE catalyzes an electroneutral exchange of anions [25]. Exit of HCO_3^- leads to the accumulation of Cl^- in the ICF compartment. Since all cells have Cl^- channels in their membrane [26], the rise in the ICF Cl^- concentration in conjunction with the usual negative voltage forces Cl^- to exit from cells (Figure 9). This export of negative voltage when Cl^- ions exit causes a less negative voltage in cells. As a result, K^+ will exit from cells if K^+ channels are open. The net effect of this flux through the AE is the export of K^+ and HCO_3^- from cells. Thus a shift of K^+ out of cells would occur in response to an inorganic acid load or a non-monocarboxylic organic acid load such as citric acid [27].

Buffering of H^+ by Intracellular Proteins

P_{HCO3}: When the P_{HCO3} is very low, there is little HCO_3^- in the ECF compartment to buffer newly added H^+ so most of these H^+ will now be bound to intracellular proteins. Hence when the P_{HCO3} is *very* low and if there is a possibility that it may decline even further, this may be an indication to administer $NaHCO_3$. In this regard, it is also important to note the impact of very small absolute changes in the P_{HCO3} when this concentration is very low to begin with. For instance, if the fall in the P_{HCO3} is only 2 mM, but it fell from 4 mM to 2 mM, there is a doubling (100% rise) of the plasma H^+ concentration and a fall

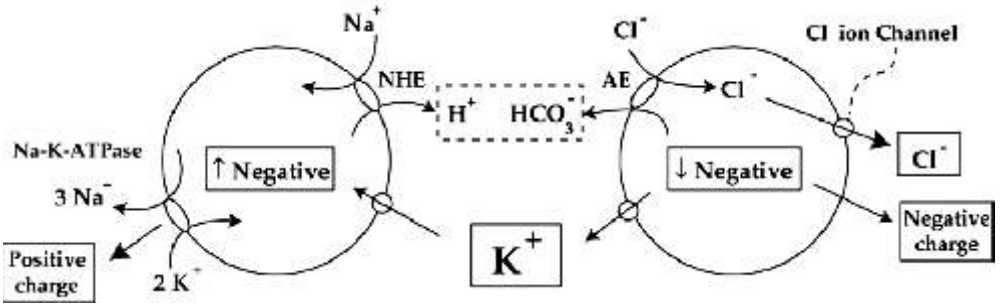

Figure 9. NHE and NE adjust the cell voltage and the P_K. The circles represent cells with their usual net negative ICF voltage. Because of the higher Na^+ concentration outside cells and the higher H^+ concentration in cells, the NHE catalyzes H^+ exit and Na^+ ion entry into cells in an electroneutral fashion (left portion). This transport requires activation by insulin or intracellular acidosis. When Na^+ ions are exported by the Na-K-ATPase, the voltage in cells becomes more negative. The net effect is to shift K^+ ions into cells. As shown on the right, because of the much higher Cl^- ion concentration outside cells, the AE catalyzes HCO_3^- exit and Cl^- ion entry into cells in an electroneutral fashion. The combination of flux through the AE and the Cl^- ion channel tends to decrease the negative ICF voltage and cause intracellular acidification and ECF alkalinization. This transporter required activation but the mechanism is not clear. The net effect is to shift K^+ ions into cells.

in plasma pH of 0.3 units if the arterial PCO_2 remains unchanged (which is likely to be the case as hyperventilation is probably already maximal). In contrast, a fall in the P_{HCO3} of 2 mM from 25 mM to 23 mM will cause only a 10% rise in the plasma H^+ concentration.

Arterial PCO_2: A high value for the arterial PCO_2 can have profound effects on the ICF pH in a patient with metabolic acidosis. For CO_2 to diffuse out of cells, intracellular PCO_2 will have to be somewhat higher than in the capillaries. The arterial PCO_2 depends on the balance between CO_2 production and its removal from the body by ventilation (Figure 7). Thus the arterial PCO_2 will be higher in a patient who cannot increase ventilation appropriately. In this case, mechanical ventilation is the most effective means to lower the intracellular pH and thereby minimize the binding of H^+ to intracellular proteins. There are several ways to assess this ventilatory response to the presence of metabolic acidosis (Table 4). Use the approximately 1 : 1 ratio between the fall in P_{HCO3} from the normal value of 25 mM and the fall in arterial PCO_2 from 40 mmHg [28]. We emphasize that these are not meant to be exact values.

CO_2 production: As an isolated event, a rise in CO_2 production rate will increase the capillary PCO_2. Similarly, a low arterial PCO_2 may also reflect a lower rate of production of CO_2 in patients who have a fixed degree of ventilation [29].

Venous PCO_2: The impact of a higher venous PCO_2 on the degree of buffering of H^+ by intracellular proteins is illustrated in Figure 7. If the venous PCO_2 is high, the intracellular PCO_2 will be even higher, which shifts the equilibrium of Equation 3 to the left, raising the H^+ concentration in the ICF so that more H^+ will bind to proteins. Three factors could lead to an elevated venous PCO_2; first, a high PCO_2 of arterial blood; second, a higher rate of metabolic production of CO_2; third, the quantity and the concentration of CO_2 that each liter of blood must carry will rise if there is a reduced rate of blood flow to an organ. It follows that in the setting of metabolic acidosis associated with reduction in ECF volume (Table 3), a very important mea-

Table 3. Metabolic acidosis classified according to extracellular fluid volume status.

Metabolic acidosis with a reduced "effective" circulating volume
– type A L-lactic acidosis (*venous* volume may not be reduced)
– diabetic or alcoholic ketoacidosis
– gastrointestinal loss of $NaHCO_3$
– metabolic acidosis and excessive loss of Na^+ in the urine
  – e.g. overproduction of hippuric acid in glue-sniffers

Metabolic acidosis with a near-normal or expanded ECF volume
Increased anion gap
– ketoacidosis of fasting or due to hypoglycemia
– toxic alcohol ingestions (methanol, ethylene glycol)
– overproduction of D-lactic acid
– renal failure

Normal anion gap
– low NH_4^+ excretion (e.g. distal RTA)
– proximal RTA

Table 4. Expected responses to primary acid-base disorders.

Disorder	Response
Metabolic acidosis	For every mM fall in P_{HCO3} from 25 mM, the arterial PCO_2 should fall by 1 mmHg from 40 mmHg.
Metabolic alkalosis	For every mM rise in P_{HCO3} from 25 mM, the arterial PCO_2 should rise by 0.7 mmHg from 40 mmHg.
Respiratory acidosis	
Acute	For every mmHg rise in arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should rise by 0.77 nM from 40 nM. Alternatively, for every 2-fold increase in arterial PCO_2, the P_{HCO3} should increase by 2.5 mM.
Chronic	For every mmHg rise in arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should rise by 0.32 nM, or the P_{HCO3} should rise by 0.3 mM from 25 mM.
Respiratory alkalosis	
Acute	For every mmHg fall in the arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should fall by 0.74 nM from 40 nM.
Chronic	For every mmHg fall in arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should fall by 0.17 mM, or the P_{HCO3} should fall by 0.4 mM from 25 mM.

sure to correct the intracellular acidosis may in fact be the aggressive restoration of the effective circulating volume.

Hypokalemia: Hypokalemia may be present in some patients with metabolic acidosis (e.g., patients with distal renal tubular acidosis (RTA) or those with diarrhea or glue sniffing). As K^+ shift from the ICF into the ECF compartment, electroneutrality must be maintained. This could be achieved if the K^+ are lost from the ICF along with intracellular anions (phosphate), or if K^+ enter and extracellular cations (Na^+ and/or H^+) exit. To the extent that there is a net exit of K^+ and entry of H^+, the degree of intracellular acidosis will become more severe and now more H^+ should be titrated by intracellular proteins. Hypokalemia may also affect the intracellular H^+ concentration by causing respiratory muscle weakness; the hypoventilation could cause a rise in arterial and thereby the tissue PCO_2.

Excretion of NH_4^+

CONCEPT 3: Generation of new HCO_3^- without H^+ occurs when NH_4^+ is excreted.

To generate new HCO_3^-, glutamine, must be metabolized in the cells of the proximal convoluted tubule (PCT) to yield NH_4^+ and the -ketoglutarate (-KG) anion [15]. Metabolism of -KG to neutral end products (CO_2 or glucose) yields HCO_3^- that are added to the body. Nevertheless, for a net gain of HCO_3^-, NH_4^+ must be made into an end product of metabolism by being excreted in the urine (Figure 5). The rate of excretion of NH_4^+ can be influenced by 2 major factors, its rate of production in the PCT and its rate of transfer to the final urine.

Production of NH_4^+: Several factors influence the rate of production of NH_4^+. It is important to recognize that there is a 1- to 2-day lag period before acidosis augments renal ammoniagenesis. In response to chronic metabolic acidosis, the rate of excretion of NH_4^+ can increase to more than 200 mmol/day [30, 31]. Hypokalemia also stimulates ammoniagenesis as it causes intracellular acidosis [32]. The converse is true for hyperkalemia. There is an upper limit on the rate of NH_4^+ production in cells of the PCT set by the rate of regeneration of ATP in these cells [33]. ATP is utilized in PCT cells primarily to provide the energy for the reabsorption of filtered Na^+ [34]. Hence patients with a low GFR filter less Na^+ and they have a lower rate of reabsorption of Na^+ in the PCT. This lessens the need to regenerate as much ATP so the rate of production of NH_4^+ is lower in these patients. Rarer causes of a low rate of production of NH_4^+ are low levels of glutamine in plasma (malnutrition) [35] or if another fuel is oxidized by the cells of the PCT for regeneration of ATP (e.g., an excessive supply of ketoacids or fatty acids as in patients receiving total parenteral nutrition) [36]. Patients with isolated proximal RTA may have a lower rate of NH_4^+ production due to an alkalinized PCT cell pH, the underlying pathophysiology in this condition [37].

Transfer of NH_3 into the urine: NH_4^+ produced in cells of the PCT is secreted into its lumen, at least in part, by replacing H^+ on the Na^+/H^+ exchanger (NHE-3), making it a Na^+/NH_4^+ exchanger [38]. Reabsorption of NH_4^+ in the medullary thick ascending limb (mTAL) of the loop of Henle (LOH) occurs when NH_4^+ replaces K^+ on the Na^+, K^+, 2 Cl^-cotransporter [39]. This provides the "single effect" for the medullary recycling of NH_4^+ required for the establishment of a high concentration of NH_4^+ and NH_3 in the medullary interstitium (Figure 5). The function of this medullary interstitial NH_4^+/NH_3 system in our opinion is to prevent the excretion of urine with too low a pH [40]. An important factor that influences the transfer of

NH_4 from the medullary interstitial compartment to the urine is the secretion of H^+ in the distal nephron. This H^+ secretion provides the luminal substrate for an NH_4^+/H^+ ion exchanger [41]. This NH_4^+/H^+ exchanger results in the net addition of NH_3 into the lumen.

H^+ secretion in the distal nephron is mediated primarily by an H^+-ATPase, but it may also occur by an H^+/K^+-ATPase. Distal H^+ secretion by the H^+-ATPase is an electrogenic process that tends to create a lumen positive voltage [42]. Because the lumen of the MCD can only maintain a small positive voltage [43], for H^+ secretion to continue, either an anion (like Cl^-) must be secreted along with H^+ or a cation like Na^+ or K^+ must be reabsorbed.

H^+ secretion also occurs by an H^+/K^+-ATPase, but only if H^+ acceptors are available in the lumen of the distal nephron. These luminal H^+ acceptors are HCO_3^- and NH_3. Luminal HCO_3^- can be high if its reabsorption by upstream nephron segments was diminished or if HCO_3^- was secreted into the lumen of the MCD by a Cl^-/HCO_3^- anion exchanger [25]. In this latter circumstance, there is a net reabsorption of K^+ and Cl^-; hence this combination of ion exchangers may be important for K^+ homeostasis under conditions of K^+ depletion [44]. If both the H^+/K^+-ATPase and the Cl^-/HCO_3^- anion exchanger were active simultaneously, the urine PCO_2 should be very high. When NH_3 is available to accept H^+ secreted by the H^+/K^+-ATPase, its overall function could be to reabsorb K^+ and/or excrete NH_4^+.

Importance of the Urine pH to Avoid Kidney Stone Formation

All the water-soluble waste products and all the ions and water ingested in excess of needs must be excreted in the urine without forming precipitates. One of the most important renal physiological functions is to excrete urine with a composition that makes ions and organic materials sufficiently soluble to avoid kidney stone formation. Key to this aim is to have independent regulation of the urine pH – select a value that is close to 6.0 to achieve this aim [45] (Figure 10). Excreting urine at

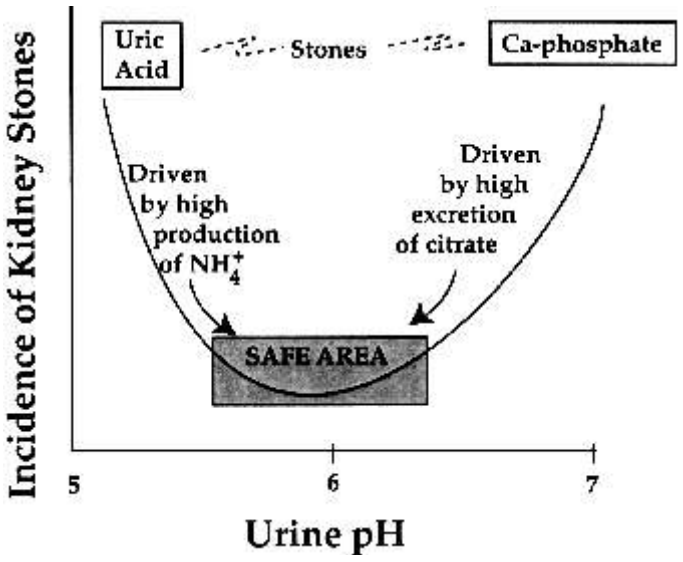

Figure 10. Urine pH and kidney stones. The safest urine pH to avoid kidney stones is close to 6. Below this value, uric acid stones are most likely to form. Ca-phosphate stones precipitate in alkaline urine. By driving NH_4^+ excretion with a high distal H^+ secretion, a considerable quantity of H^+ can be eliminated at a urine pH close to 6.0. By excreting organic anions rather than HCO_3^-, a considerable quantity of HCO_3^- can also be eliminated at a urine pH close to 6.0 (see Figure 2).

this pH must not sacrifice acid-base balance. This in turn means that with a large, chronic acid load, the excretion of NH_4^+ should be maximally high at a urine pH of close to 6 (see reference Kamel et al. 1998 [46] for more discussion). Similarly, when an alkali load is ingested, it must be excreted without obligating a large excretion of HCO_3^- and thereby a high urine pH [9, 11] – this latter topic will be discussed in more detail when $CaHPO_4$ stones are considered below.

Avoiding uric acid kidney stones: Uric acid is the waste product of purine metabolism [47]. The free acid form, uric acid, rather than total urates is the critical component for kidney stone formation because uric acid is sparingly soluble in water (Equation 4). Because the pK of uric acid in the urine at 37ºC is close to 5.3 [47], precipitation of uric acid can be avoided without increasing the urine volume by raising the urine pH to 6 at the same total urate excretion rate [48].

$$Urate^- + H^+ \quad \text{Uric acid (pK 5.3)} \qquad (4)$$

Avoiding $CaHPO_4$ kidney stones: All the ionized Ca^{2+} absorbed from the GI tract of an adult is excreted in the urine in steady state [49]. The chemistry of Ca^{2+} and HPO_4^{2-} in the urine is the same as in the body [50], but with one exception. A metabolic equivalent of HCO_3^- in acid-base terms, citrate [14], can chelate ionized Ca^{2+} in the urine, forming a soluble ion complex and thereby minimize the risk of $CaHPO_4$ kidney stone formation. This excretion of citrate rises with an alkali load [14], a time when urine $H_2PO_4^-$ is converted to HPO_4^{2-} – i.e., when the urine pH rises towards the pK of the phosphate buffer system (pH 6.8). In this context, the body disposes of the usual alkali load of the diet by forming an organic acid such as citric acid [9, 11]. The H^+ of citric acid titrate HCO_3^-. The citrate anions rather than an appreciable amount of HCO_3^- are excreted in the urine so that the urine pH remains close to 6.0 without sacrificing acid-base balance [48] (Figure 10). Excreting citrate rather than HCO_3^- when there is a dietary alkali load chelates Ca^{2+} in the urine, lessening the risk of Ca-containing kidney stones in alkaline urine [51].

Tests Used at the Bedside to Estimate NH_4^+ in the Urine

The first step to evaluate the renal response to chronic metabolic acidosis in a patient is to examine the rate of excretion of NH_4^+. Since most routine biochemical laboratories do not provide a direct assay for the concentration of NH_4^+ in the urine (U_{NH4}), clinicians usually employ the following indirect tests to *estimate* U_{NH4}. To convert the U_{NH4} to an excretion rate, one needs to know the urine flow rate or divide the U_{NH4} by the urine creatinine concentration. Normal adults excrete close to 20 mg of 200 mol of creatinine per kg body weight [52].

The urine net charge: The sum of the concentrations of urinary cations and anions must be equal. The major urine cations are Na^+, K^+, and NH_4^+, and the major urine anion is Cl^- (although there are also modest concentrations of SO_4^{2-}, phosphate, HCO_3^- and organic anions). The urine net charge provides a qualitative *estimate* of the U_{NH4} providing that the major anion excreted with NH_4^+ is Cl^- (Equation 5, Figure 11). Hence if the U_{NH4} is appropriately high, the U_{Cl} should be appreciably greater than the sum of the $U_{Na} + U_K$, and the urine net charge is said to be *negative*. On the other hand, with a low U_{NH4}, the U_{Cl} is less than the sum of the $U_{Na} + U_K$. In this case, the urine net charge is said to be *positive*, suggesting that a defect in NH_4^+ excretion is at least contributing to the pathogenesis of metabolic acidosis. Be careful. This will not be true if an

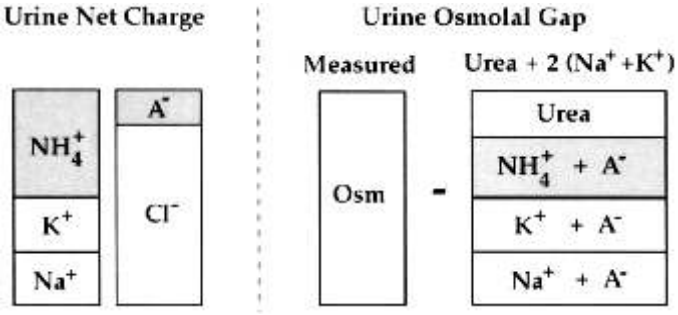

Figure 11. Use of the urine net charge and urine osmolal gap to reflect the concentration of NH_4^+ in the urine. The urine net charge is shown in the left portion of the figure and the urine osmolal gap is shown in the right portion of the figure. The components needed to calculate the U_{NH4} are depicted by the clear areas. Reproduced with permission [187].

anion other than Cl^- accompanied U_{NH4}. Some examples of these non-Cl^- urine anions are hippurate, -HB, salicylate, organic anions, and anions of drugs such as penicillin-type antibiotics given in high dosage. In such cases, one must use the urine osmolal gap to estimate U_{NH4}.

$$\text{Urine net charge} = U_{Na} + U_K - U_{Cl} \quad (5)$$

The urine osmolal gap: The urine osmolal gap is the best indirect test to estimate the U_{NH4}. The rationale for the urine osmolal gap is also depicted in Figure 11. The major osmoles in the urine are urea and electrolytes; occasionally, glucose may be present in the urine in high concentrations. The contribution of electrolytes is approximately equal to twice the sum of the concentrations of the major cations, Na^+, K^+ (since each cation is accompanied by an anion). Therefore, the total urine osmolality (U_{osm}) can be approximated as shown in Equation 6 in which the concentration of all the substances in the urine is given in mM terms as described earlier. A significant difference between the measured and calculated U_{osm} indicates the presence of an NH_4^+ salt in the urine. The U_{NH4} is half the urine osmolal gap. The rate of excretion of NH_4^+ is then obtained by multiplying this approximate concentration by the urine flow rate or estimated from the urine creatinine concentration and its excretion rate [52]. If this is substantially less than 3 mmol NH_4^+/kg/day, then the kidneys are at least a contributing factor to the degree of metabolic acidosis because there is a lower than expected rate of excretion of NH_4^+.

$$\text{Calculated } U_{osm} = U_{Urea} + U_{Glu} + 2\,U_{Na} + 2\,U_K$$
$$U_{NH4} = 0.5 \times$$
$$(\text{measured } U_{osm} - \text{calculated } U_{osm}) \quad (6)$$

Tests to Detect the Basis for the Low Rate of Excretion of NH_4^+

Use of the urine pH: In patients with chronic metabolic acidosis, a low rate of excretion of NH_4^+ could be due to decreased availability of NH_3 in the medullary interstitium or decreased H^+ secretion in the distal nephron (Figure 12). The basis for low NH_4^+ excretion can be deduced from the urine pH (Figure 13). A low value for the urine pH (< 5.3) suggests a defect in NH_4^+/NH_3 availability in the renal medullary interstitium whereas a high urine pH (> 7) suggests that the limiting step is H^+ secretion in the distal nephron (Equation 7) [53 – 57].

$$H^+ + NH_3 \quad NH_4^+ \quad (7)$$

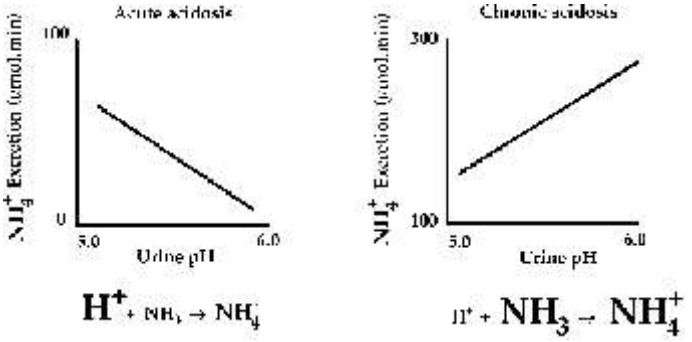

Figure 12. Use of the urine pH to detect U_{NH4}. As shown on the left, during acute metabolic acidosis, the rate of excretion of NH_4^+ is only modestly higher while the urine pH is low. This is because there is enhanced distal H^+ secretion, but a time lag before the rate of renal production of NH_4^+ is augmented. In contrast, during chronic metabolic acidosis shown on the right, the rate of renal production of NH_4^+ is so high that the availability of NH_3 in the medullary interstitial compartment provides more NH_3 in the lumen of the MCD than H^+ secretion in this nephron segment. Therefore note the much higher NH_4^+ excretion rate at a urine pH of 6. Reproduced with permission [187].

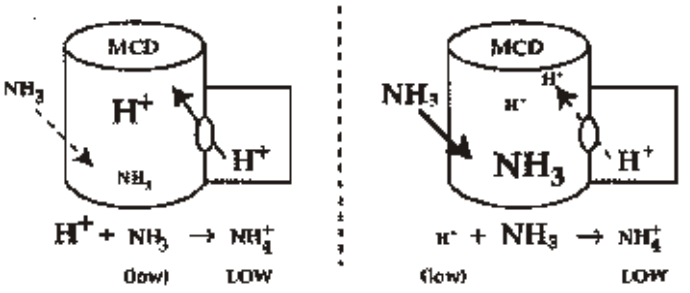

Figure 13. The urine pH reveals the basis for the low U_{NH4}. A decreased availability of NH_4^+/NH_3 in the medullary interstitial compartment is the defect shown on the left side of the figure by the dashed arrow. Its main features are a low excretion of NH_4^+ and a high urine H^+ concentration (low urine pH). A defect in distal H^+ secretion is shown by the dashed arrow in the right side of the figure. Its main features are a low excretion of NH_4^+ and a low urine H^+ concentration (high urine pH). Reproduced with permission [187].

Test for the Capacity to Synthesize NH_4^+ in the PCT

Once one knows that the rate of excretion of NH_4^+ is low in a patient who has a low urine pH, one can assess the rate of production of NH_4^+ in vivo by measuring the rate of excretion of NH_4^+ following the administration of a loop diuretic [58]. At peak diuresis, the rate of NH_4^+ excretion in a normal adult is close to 60 mol/min and this reflects the capacity for renal ammoniagenesis. A lower peak rate of NH_4^+ excretion would imply a low rate of production of NH_4^+ in PCT cells [37, 59].

Tests to Evaluate H^+ Secretion

A low rate of excretion of NH_4^+ in a patient with metabolic acidosis could be due to a defect in H^+ secretion in the PCT and/or the distal nephron.

Tests to Evaluate the Secretion of H^+ in the PCT

Some patients have metabolic acidosis associated with a lower than normal capacity to reabsorb filtered HCO_3^- [60]. Usually the site of the defect in renal H^+ secretion is in the PCT, but at times, it may also involve the distal nephron. Notwithstanding, these patients also have a reduced rate of excretion of NH_4^+ and this is a very important cause of their metabolic acidosis. To detect a defect in H^+ secretion in the PCT, one generally measures the rate of excretion of HCO_3^- and/or its reabsorption after an infusion of $NaHCO_3$. Another test that helps in this assessment is the rate of excretion of citrate at a given pH of plasma.

Fractional excretion of HCO_3^- (FE_{HCO3}): The bulk of filtered HCO_3^- is reclaimed (reabsorbed indirectly) in the PCT [61], but an appreciable portion (close to 15%) is normally reclaimed by H^+ secretion downstream in the nephron. To perform this test, enough $NaHCO_3$ is infused to raise the P_{HCO3} to 25 mM. At this point, if the FE_{HCO3} exceeds 15%, there is a defect in H^+ secretion [61, 62]. A high FE_{HCO3} could be expected if there is a very large defect in H^+ secretion in the PCT or a smaller defect in PCT H^+ secretion plus a reduced distal capacity for H^+ secretion.

Citrate excretion: The rate of excretion of citrate seems to reflect the pH in PCT cells with a higher rate of citrate excretion if these cells have a more alkaline pH in PCT cells. The rate of excretion of citrate is very low during all forms of metabolic acidosis except in patients with the isolated form of proximal RTA where there is an appreciable degree of citraturia despite metabolic acidosis [63]. This led to the speculation that an alkaline PCT cell is the underlying lesion causing low HCO_3^- reabsorption, low NH_4^+ production, and citraturia in these patients [37]. The rate of excretion of citrate in children and adults consuming their usual diet is close to 400 mg/g creatinine [14, 64]. To ensure that citraturia reflects an alkaline PCT cell rather than a component of a more generalized PCT dysfunction (Fanconi syndrome), citraturia should disappear following a small additional acid load [65].

Tests to Evaluate the Secretion of H^+ in the Distal Tubule

If the PCO_2 in alkaline urine is 70 mmHg or higher, a major defect in distal H^+ secretion is unlikely [66] (Figure 14). Nevertheless, there

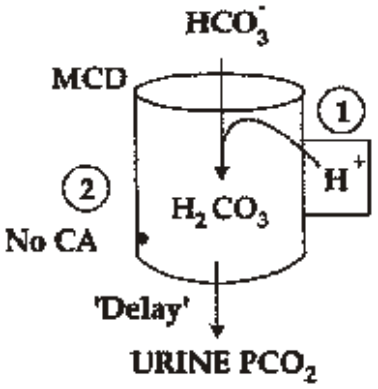

Figure 14. The urine PCO_2. When $NaHCO_3$ is given, there is a large delivery of HCO_3^- to the distal nephron so this HCO_3^- is virtually the only H^+ acceptor in its lumen. Because there is no luminal carbonic anhydrase (CA), the H_2CO_3 formed will be delivered downstream and form CO_2 plus water. Thus if the U_{PCO2} is appreciably higher than the plasma PCO_2, this provides evidence for distal H^+ secretion. Reproduced with permission [187].

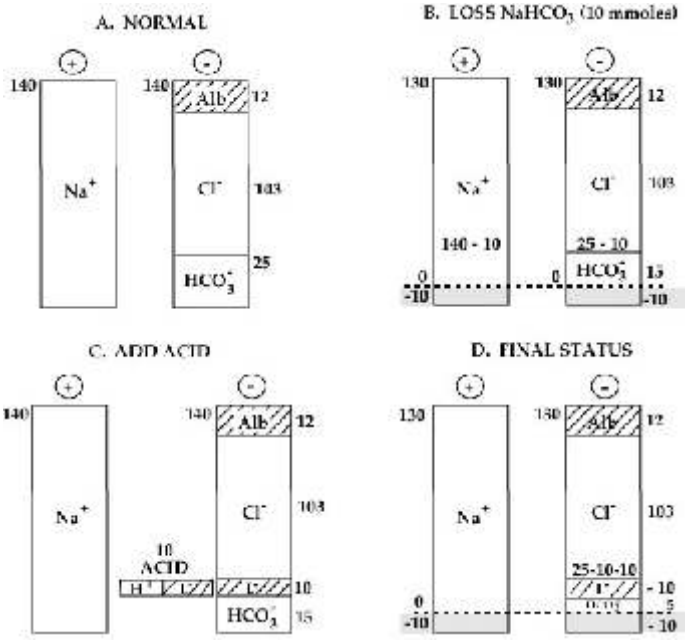

Figure 15. Mixed acid-base disturbance: Recognizing 2 types of metabolic acidosis. The sum of the valences on cations and anions in plasma are always equal. In this example, the missing anions (due largely to the anionic charge on albumin shown by the hatched symbol) are constant at 12 mEq/l; this value is 16 mEq/l if K^+ is included in the sum of cations in plasma. When Na^+ and HCO_3^- are lost (shaded area in panels B and D), there is no change in the plasma anion gap. When L-lactic acid is added, there is a fall in the concentration of HCO_3^- together with an equal rise in the plasma anion gap (panel C). The combination of both types of metabolic acidosis is shown in panel D.

are other factors such as a poor renal concentrating ability (low medullary interstitial PCO_2) that may cause the urine PCO_2 to be lower despite an intact distal H^+ secretion [67].

Detecting Mixed Acid-base Disorders

More than one acid-base disturbance can be present at one time. We shall illustrate how to identify the simultaneous presence of several acid-base disturbances from the history, physical examination, and laboratory results (Figure 15).

Clinical example: A 24-year-old person had severe diarrhea that resulted in a deficit of $NaHCO_3$ (Figure 15B). Because of the continuing loss of Na^+, his ECF volume became markedly contracted. As a result of the very low circulating volume, there was not enough oxygen delivery to tissues to meet their demand so anaerobic production of ATP was stimulated. This results in a net production of L-lactic acid. This accumulation of 10 mmol of L-lactate anion per liter of plasma should raise the plasma anion gap by 10 mEq/l (Table 4, Figure 15C). Simultaneously, the 10 mmol of H^+ added per liter will lower the P_{HCO3} by 10 mmol/l (Equation 8).

$$10\,\text{L-lactate}^- + 10\,H^+ + 15\,HCO_3^- \quad 10\,CO_2 + 10\,H_2O + 10\,\text{L-lactate}^- + 5\,HCO_3^- \qquad (8)$$

Continuing with this scenario, the release of aldosterone (due to a contracted ECF volume) stimulates the excretion of K^+ [68]. As a result, a deficit of K^+ occurs and this could lead to muscular weakness. If the respiratory muscles are involved, there may be an inability to lower the arterial PCO_2 to the expected degree. In summary, by working backwards beginning at the far right of Table 5, each of the 3 acid-base disorders can be identified.

– Respiratory acidosis: The PCO_2 in blood should be as low as possible (less than 20

Table 5. Identification of a mixed acid-base disorder. For details, see text. The value for albumin in plasma is 4 g/dl (40 g/l), a normal level which does not change throughout the course of illness in this patient. Hypoventilation in this case is due to a deficit of K^+. H●L = L-lactic acid.

Plasma		Normal	Loss $NaHCO_3$ (10 mM)	Gain H●L (10 mM)	Effect of hypoventilation
pH		7.40	7.30	7.13	6.83
HCO_3^-	mM	25	15	5	5
Anion gap	mEq/l	12	12	22	22
PCO_2	mmHg	40	30	15	30

mmHg) with such a low value for the P_{HCO3} (5 mM). Hence the arterial PCO_2 is too high for this clinical setting.

– Metabolic acidosis due to a gain of acid: The elevated value for the anion gap of 10 mEq/l with a normal concentration of albumin in plasma suggests that 10 of the 20 mM fall in P_{HCO3} was due to the added L-lactic acid.

– Metabolic acidosis due to loss of $NaHCO_3$: The fact that the fall in the P_{HCO3} is much greater than the rise in the plasma anion gap suggests a deficit of $NaHCO_3$. This deficit of $NaHCO_3$ is even larger than what is apparent from this calculation because of the significant ECF volume contraction (HCO_3^- concentration vs HCO_3^- content, Table 10).

Clinical Disorders

Metabolic Acidosis

Definition: In metabolic acidosis, there is a fall in the plasma pH and P_{HCO3}. Because other primary acid-base abnormalities may coexist, the plasma pH and/or P_{HCO3} may not be low. For example, if respiratory alkalosis is also present, the pH will be higher; if metabolic alkalosis is also present, the P_{HCO3} and plasma pH may not be low. Therefore clues from the history and physical examination together with additional laboratory data (plasma anion gap) must be integrated to know whether metabolic acidosis is present.

Clinical Classification

We divide the causes of metabolic acidosis into two subgroups, those with overproduction of acids and/or those in which there is a loss of $NaHCO_3$ (Table 6).

Overproduction of acids: When an acid (HA) is added to the body, the vast majority of H^+ are buffered by the bicarbonate buffer system (BBS) [4] and this leads to the loss of HCO_3^- together with a gain of new anions (A^-) (Figure 4). Quantitatively, for every mEq of HCO_3^- lost, there will be an equivalent net gain of A^-. Factors such as the volume of distribution of anions versus H^+, a change in the ECF volume, and the renal handling of these anions will affect the 1 : 1 ratio between the fall in the P_{HCO3} and the rise in plasma anion gap (Table 7). With a decrease in the ECF volume, the concentration of both new anions

Table 6. Mechanisms responsible for the development of metabolic acidosis.

A) Acid gain
- **(i) With retention of anions in plasma:**
  - L-lactic acidosis (hypoxia, problems with pyruvate metabolism)
  - Ketoacidosis (relative insulin lack and low GFR or CNS function)
  - Toxic alcohol ingestion (e.g., methanol, ethylene glycol)
  - D-lactic acidosis (and other organic acids produced by gastrointestinal bacteria)
  - Ingested acids
  - Pyroglutamic acidosis
- **(ii) With a high rate of excretion of anions in urine:**
  - Glue-sniffing (hippuric acid overproduction)
  - Diabetic ketoacidosis with excessive ketonuria

B) $NaHCO_3$ loss
- **(i) Direct**
  - Loss via the GI tract (e.g., diarrhea, ileus, fistula)
  - Loss in the urine (proximal RTA or low carbonic anhydrase II or IV activity)*
- **(ii) Low urinary excretion of NH_4^+ (look at urine pH to categorize further)**
  - **(a) Low urine NH_3 (urine pH ~ 5) = Problem with PCT ammoniagenesis:**
    Decreased GFR, hyperkalemia, alkaline pH in PCT cells, decreased glutamine availability, fuel competition (e.g., TPN)
  - **(b) Defect in net distal H^+ secretion (urine pH often ~ 7):**
    H^+ ATPase defect or alkaline -intercalated cells (e.g., carbonic anhydrase II deficiency)
    H^+ back-leak (e.g., amphotericin B)
    HCO_3^- secretion in the collecting ducts (anion exchanger trafficking disorder)
  - **(c) Problem with both distal H^+ secretion and NH_3 availability (urine pH ~ 6):**
    Diseases involving the renal interstitial compartment

*These patients also have a low rate of excretion of NH_4^+.

Table 7. Content vs concentration of $HC0_3^-$ in the ECF compartment. An 8-year-old 20 kg female presented with an extremely high P_{Glu} (2,000 mg/dl, 110 mM), a venous plasma pH of 7.19, a P_{HCO3} of 25 mM, and a severely contracted ECF volume (2 vs her normal 4 l) [69]. Metabolic acidosis is present because of the reduced content of HCO_3^- in her ECF compartment (H^+ + -HB^- + HCO_3^- anion gap + CO_2 + H_2O). Reproduced with permission [187].

	ECF (l)	P_{HCO3} (mM)	ECF HCO_3^- content (mmol)	Plasma anion gap (mEq/l)
Normal state	4	25	100	12
Hyperglycemia	2	25	50	24

and HCO_3^- will rise. Thus there will be a larger increase in the unmeasured anion gap and a smaller fall in the P_{HCO3} [69], disturbing the expected 1 : 1 ratio in these parameters.

In most cases where metabolic acidosis is associated with an increased value for the anion gap in plasma, there is an overproduction of acids where many of the anions produced

along with H^+ are retained in the ECF. The major exception to this rule is renal failure because in this setting, metabolic acidosis is present with an increase in the plasma anion gap, but there is no excess production of acids. On the other hand, metabolic acidosis caused by an excessive production of acids need not be accompanied by a significant rise in the anion gap in plasma if the accompanying anion is rapidly excreted in the urine (e.g., hippurate anion in glue sniffing [21]).

There are many different causes for the development of metabolic acidosis, each having a specific implication for therapy. In most cases, the rise in the concentration of H^+ per se is not the major threat to survival; those causes associated with acute potentially life-threatening consequences are listed in Table 8. Many of the causes of metabolic acidosis and an increased plasma anion gap are associated with a reduced "effective" ECF volume (diabetic ketoacidosis (DKA), alcoholic ketoacidosis, and most cases of type A L-lactic acidosis, Table 3). Should one find a relatively normal ECF volume, the basis for the metabolic acidosis is usually renal failure, toxic alcohol ingestion (methanol or ethylene glycol), or possibly excessive production of acids such as D-lactic acid by bacteria in the gastrointestinal (GI) tract.

Loss of $NaHCO_3$

In this type of metabolic acidosis, almost no new anions are present in plasma. There are 2 major groups for this type of metabolic acidosis, one is the direct loss of $NaHCO_3$ and the other is an indirect loss of $NaHCO_3$ due to a low rate of excretion of NH_4^+ (Figure 4).

Loss of $NaHCO_3$ via the GI tract: The most common site for the loss of $NaHCO_3$ is via the GI tract. While $NaHCO_3$ may be lost in diarrhea fluid, for an appreciable degree of chronic metabolic acidosis to be sustained, there is usually a simultaneous defect in NH_4^+ excretion by the kidney. In more detail, in a 70 kg adult with chronic metabolic acidosis and normal kidneys, the rate of excretion of NH_4^+ would be close to 200 mmol per day. If 1 liter of diarrhea solution contains 50 mmol of HCO_3^-, this GI loss would have to be about 4 liters per day to cause a continuing fall in the P_{HCO3}. The deficit of Na^+ would be enormous and life-threatening without a large input of NaCl. Hence it follows that chronic acidosis in this setting implies either a very large or an acute GI losses, a renal problem with NH_4^+ excretion (e.g., due to low GFR), and/or overproduction of organic acids via the GI tract (Equation 9) [70, 71].

$$Na^+ + HCO_3^- + H^+ + \text{D-lactate}^- \quad Na^+ + \text{D-lactate}^- + CO_2 + H_2O \qquad (9)$$

Indirect loss of $NaHCO_3$: A low rate of excretion of NH_4^+ is the key finding in patients with distal RTA [56]; it is also a prominent feature in certain patients with proximal RTA [37]. In a patient with metabolic acidosis, with no increase in the plasma anion gap, and a low rate of excretion of NH_4^+ (Figure 15, left-hand side), the basis for low NH_4^+ excretion can be deduced from the urine pH. If the urine pH is greater than 7, one should suspect a defect in H^+ secretion. The PCO_2 in alkaline urine can be used to assess distal H^+ secretion (Figure 14) [66] and the FE_{HCO3} can be used to assess proximal H^+ secretion. A high rate of excretion of citrate in a patient with metabolic acidosis suggests that an alkaline PCT cell could be the cause of diminished PCT H^+ secretion [37]. In contrast, if a patient had similar findings to the above, but had a low value for the urine pH (e.g., < 5.3), this would suggest that there is a defect in NH_3 availability in the renal medullary interstitial compartment

Table 8. Threats to life in association with metabolic acidosis.

Setting of acidosis	Threat to life	Clinical clues
L-lactic acidosis due to low cardiac output (shock)	"Energy crisis", H^+ load	Low plasma pH, high plasma anion gap, high $P_{Lactate}$
Renal failure	Hyperkalemia	Low GFR, high plasma anion gap
Distal RTA, diarrhea, treatment of DKA	Hypokalemia	Normal plasma anion gap, arrhythmias, muscle weakness
Methanol or ethylene glycol intake	Toxic products	History, high plasma anion gap, high plasma osmolal gap
DKA or, alcoholic ketoacidosis	Low ECF volume, rarely acidosis per se	Type 1 diabetes mellitus, ethanol, P_{Glu}, ketoacid screen

(Figure 13). The usual causes for the low NH_4^+/NH_3 are a low GFR and/or hyperkalemia. In their absence, we would look for low levels of glutamine in blood and/or a high level of fat-derived fuels (e.g., patients on total parental nutrition) because these fuels compete with glutamine as the source for regeneration of ATP in the cells of the PCT. If none of these is present, we would suspect an alkaline proximal cell pH. This entity of an alkaline proximal ICF pH remains speculative because there are no hard data in humans and suitable experimental models in animals are lacking.

Loss of "Potential" HCO_3^-

In some patients, there is excessive loss of the conjugate base of the acid in the urine (or in stool). While overproduction of acids is the major basis for the acidosis in these patients, yet the loss of these anions in the urine represents the loss of potential HCO_3^- as their metabolism could have resulted in the removal of H^+ (Figure 4, [72]).

Likelihood of a Major Threat to Life

Disorders that cause metabolic acidosis can harm patients through a variety of mechanisms (Table 8). We shall consider 4 major categories:

Very Fast Rate of Production of H^+

In essence, the only condition associated with extremely rapid net production of acid is L-lactic acidosis due to hypoxia (Table 2). The threat here is that ATP may not be regenerated quickly enough. Quantitatively, the rate of acid addition can be approximated by

Table 9. Causes of metabolic acidosis associated with hyperkalemia. Specific disorders causing hyperkalemia in patients with metabolic acidosis are described. In addition, if tissue necrosis has occurred in a patient with metabolic acidosis, hyperkalemia may also be present.

Cause	Pathophysiology	Total K^+ content
Renal failure	Low renal excretion of K^+ (and NH_4^+)	High
Low aldosterone bioactivity	Low renal excretion of K^+ (and NH_4^+)	High
DKA	Insulin deficiency leads to shift of K^+ out of the ICF	Low

noting the rate of increase in the plasma anion gap and the rate of excretion of anions in the urine.

H^+ Binding to Intracellular Proteins

The important factors here are not only the magnitude of H^+ load, but also the tissue PCO_2 as this determines the distribution of buffering of H^+ load between the BBS and intracellular proteins. A high venous PCO_2 implies that the tissue PCO_2 is also high and that more H^+ are buffered by intracellular proteins. Hence it follows that in the setting of metabolic acidosis associated with a low cardiac output, a very important measure to correct the intracellular acidosis is aggressive restoration of the cardiac output (Figure 7). In addition, if the arterial PCO_2 is not low enough, mechanical ventilation is essential.

Coexisting Problems of K^+ Balance

Many of the risks associated with metabolic acidosis may come about through associated disturbances of K^+ balance. Both hyperkalemia and hypokalemia may occur (Table 9). We shall be succinct here because issues concerning K^+ are discussed in the accompanying Chapter on K^+.

Hyperkalemia may be involved in the etiology of metabolic acidosis, because hyperkalemia impairs NH_4^+ excretion [32]. In contrast, if metabolic acidosis is seen in the setting of renal failure, a low excretion of K^+ and hyperkalemia may be present. Hyperkalemia is commonly seen in the setting of DKA despite the total body K^+ deficit, because K^+ tend to shift out of cells during insulin deficiency [73]. Finally, tissue necrosis or ischemia can lead to both L-lactic acidosis and release of K^+ from cells. Regardless of the pathophysiology, hyperkalemia can be life-threatening due to cardiac arrhythmias, and must be aggressively treated. Fortunately, one of the measures employed in the therapy of DKA, insulin, enhances K^+ entry into cells, and therefore reduces the degree of hyperkalemia.

Hypokalemia may occur either in association with the chronic metabolic acidosis of distal RTA, diarrhea, or metabolic acidosis caused by toluene (e.g., glue sniffing). Hypokalemia may also occur as a complication of insulin therapy in patients with DKA. Because insulin causes K^+ to enter cells (Figure 9), it may unmask the total body K^+ deficit and lead to the life-threatening complications

Table 10. Factors to consider in the use of $NaHCO_3$.

A. Factors favoring the use of $NaHCO_3$
- Hyperkalemia.
- P_{HCO3} less than 5 mM.
- Absence of an anion that can be metabolized into HCO_3^- (longer term consideration).
- Low likelihood that kidneys will be able to excrete NH_4^+ at a high rate (longer term issue).
- Independent benefit likely to arise (e.g., in salicylate overdose to limit entry of salicylate into brain cells and to favor its urinary excretion).
- High net rate of H^+ production (e.g., inability to rapidly reverse hypoxic L-lactic acidosis).

B. Factors that suggest a danger for the use of $NaHCO_3$
- Hypokalemia.
- Coincident use of insulin in a patient with a large K^+ deficit.
- Elevated ECF volume.
- Hypernatremia (minor).

of acute hypokalemia, particularly cardiac arrhythmias.

Specific problems related to the cause of the acidosis: In fact, in some of the causes of metabolic acidosis, the acidosis serves as a marker or a "symptom" of a serious underlying disease (e.g., methanol or ethylene glycol toxicity, Table 8). Clearly, these underlying processes must be addressed with specific therapy to avoid the adverse consequences that are independent of the acidosis.

Management

The management of a patient with metabolic acidosis requires a consideration of both general measures that are applicable to most patients as well as attention to specific issues relative to the cause of the disorder. We shall focus initially on the use of alkali because the use of mechanical ventilation was considered earlier, and treatments to deal with hyperkalemia or hypokalemia will be considered in the Chapter on K^+.

One cannot draw a definitive conclusion as to whether $NaHCO_3$ should or should not be used to treat a patient with metabolic acidosis because there are no firm data upon which to base this conclusion. Suggestions for and against the use of $NaHCO_3$ are summarized in Table 10.

Arguments Favoring the Use of $NaHCO_3$

It seems intuitively obvious that at some point, too many H^+ may become bound to proteins and compromise cellular functions. For example, myocardial contractility in vitro [74] and binding of adrenaline to its receptors are decreased when the fall in pH is large [75]; these effects may be reversed by lowering the concentration of H^+. Notwithstanding, the administration of $NaHCO_3$ does not seem to enhance the contractility of the ischemic myocardium in vivo [76].

There are data in experimental animals that might help. The administration of a large dose of $NaHCO_3$ appeared to be beneficial in the setting of hypoxic L-lactic acidosis in rats induced by ventilation with a hypoxic gas mixture. The survival period in these rats was extended even though $NaHCO_3$ led to an enhanced rate of production of L-lactic acid [77]. If these data apply to humans with hypoxia-induced L-lactic acidosis, the admin-

istration of $NaHCO_3$ might be viewed as a temporary measure that "buys time" to allow for more direct interventions to deal with the underlying cause(s) for the metabolic acidosis to be employed. Nevertheless, one must not administer too much $NaHCO_3$ because it may lead to the development of pulmonary edema unless very high rates of Na^+ removal could be achieved.

In a patient who has metabolic acidosis due to a low rate of excretion of NH_4^+, metabolic acidosis will persist unless $NaHCO_3$ is given. In this case, one must give enough $NaHCO_3$ to titrate H^+ that have accumulated, then maintain that person on enough alkali to match the net positive H^+ balance (usually 20 – 40 mmol/day in an adult).

Arguments Against the Use of $NaHCO_3$

Increased production of CO_2

When $NaHCO_3$ is administered, HCO_3^- reacts with H^+ and CO_2 is produced. Some have argued that this represents an important deleterious effect of HCO_3^- therapy because this CO_2 can enter cells and cause a paradoxical acidification of the ICF. This is a circular argument because if the source of the H^+ that titrate the administered HCO_3^- is H^+ bound to intracellular proteins (Figure 7), the ICF should have been alkalinized and not acidified. In contrast, if the source of these H^+ was due to the production of ATP in the process of anaerobic glycolysis, stimulation of L-lactic acid production by alkali could also be beneficial because it was accompanied by the conversion of ADP to ATP [77]. A possible acute danger in this latter case could occur if some of the CO_2 produced was retained because pulmonary function was not adequate or mechanical ventilation was not appropriately adjusted.

Concern about the possible adverse effects of enhanced production of CO_2 following therapy with $NaHCO_3$ in the acidotic patient prompted the development of carb-bicarb ($Na_2CO_3 \bullet 2(NaHCO_3)$). The titration of 4 mmol of H^+ by $NaHCO_3$ leads to the production of 4 mmol of CO_2, whereas similar buffering with carb-bicarb leads to the production of 3 mmol of CO_2. Since metabolic production of CO_2 is normally close to 10 mmol/min, and the rate of alkali administration might be close to 4 mmol/min during very aggressive alkali therapy, the difference in CO_2 production rate in fact will only be from 14 to 13 mmol/min with $NaHCO_2$ versus carb-bicarb, a trivial difference. There has been only limited clinical experience with this agent in patients with a severe degree of metabolic acidosis, the only setting in which it is rational to test it.

Failure to Detect Back-titration of Non-bicarbonate Buffers

Another argument against the use of $NaHCO_3$ or carb-bicarb to treat patients with a severe degree of metabolic acidosis comes from experiments in rats. The administered alkali to rats pretreated with HCl failed to yield an acute and significant back-titration of non-bicarbonate buffers [78]. This, however, could have been because of a rise in tissue PCO_2.

Fall in Concentration of Ionized Ca^{2+}

This occurs because addition of HCO_3^- leads to very rapid production of carbonate and precipitation of $CaCO_3$. It has been suggested that a fall in concentration of ionized Ca^{2+} in the interstitial fluid compartment might depress myocardial contractility [79]. Never-

theless, this might be more apparent than real if the HCO_3^- administered does not raise the P_{HCO3} markedly. If this were to be a problem, it should have been very obvious in situations where carb-bicarb was used because with carb-bicarb, carbonate is added directly.

Hypokalemia

Hypokalemia could be a problem when $NaHCO_3$ is given, especially if there is total body K^+ depletion as seen in patients with DKA [80 – 82], glue sniffers [21], or certain patients with distal RTA. The presence of a low P_K should prompt one to avoid the use of $NaHCO_3$, at least until the P_K has returned toward the normal range, or only to use it along with an appropriate amount of K^+ to avoid a cardiac arrhythmia (see accompanying Chapter on K^+).

ECF Volume Overload and Hypernatremia

This is only a problem in patients with metabolic acidosis who have an expanded ECF volume (patients with renal failure), in patients with a compromised circulation (cardiogenic shock), or those where enormous amounts of alkali might be used (e.g., hypoxic lactic acidosis). Hypernatremia may be produced and/or exacerbated if hypertonic $NaHCO_3$ is given.

Enhanced Production of L-lactic Acid

When $NaHCO_3$ is given to patients with L-lactic acidosis, the rate of production of L-lactic acid increases. This however may be considered beneficial if it reflects an increased rate of regeneration of ATP in vital organs [77], and if the H^+ so-produced are titrated by the BBS and not by intracellular proteins.

Rebound Metabolic Alkalosis

In metabolic acidosis due to overproduction of H^+ and anions (L- or D-lactate, or -hydroxybutyrate and acetoacetate), the acidosis will be improved when these anions are metabolized to HCO_3^-. If all the anions are converted to HCO_3^- and the patient also received $NaHCO_3$, the final plasma P_{HCO3} could be higher than normal if renal excretion of HCO_3^- did not occur [83]. The main clinical significance of rebound metabolic alkalosis is primarily when patients are being weaned from a mechanical ventilator, and the impact of HCO_3^- on the renal excretion of K^+, which can further exacerbate hypokalemia [84].

Recommendations

One must individualize the decision for each patient, balancing potential benefits versus adverse effects. None of these factors is an absolute indication or contraindication, but by examining each of them, it should be possible to make a reasonable decision. If the decision is made to administer $NaHCO_3$, an equally difficult issue is how much to give and how fast it should be given. It is important to recognize that as the baseline P_{HCO3} falls, a progressively greater amount of added H^+ are buffered on intracellular proteins. Therefore, when $NaHCO_3$ is given, the hope is that much of it will titrate these intracellular H^+, and will effectively disappear as CO_2 and water, and therefore the increment in the P_{HCO3} will be small. Moreover, CO_2 removal by the lungs

Table 11. Ketoacid turnover during chronic fasting. Values are presented as mmol/day.

Ketoacid metabolism	Organ	Turnover
Net production	Liver	1500
Oxidation	Brain	750
	Kidney	250
	Muscle, etc.	200
Conversion to acetone	?	150
Excretion	Kidney	150

Table 12. Causes of ketoacidosis.

1. Diabetic ketoacidosis
– usually Type 1 or IDDM; rarely Type 2 or NIDDM
– damage to -cells of the pancreas
– pancreatic destruction as in hemochromatosis

2. Alcoholic ketoacidosis
– low insulin due to low ECF volume (-adrenergic effect)
– metabolism of ethanol to ketoacids
– lower oxidation of ketoacids in brain (sedative effect of ethanol), and kidneys (low GFR)

3. Low stimulus to pancreatic -cells because of hypoglycemia
– starvation
– low production of glucose in the liver (e.g. glycogen storage disease or inhibition of gluconeogenesis)

4. High production of acetic and butyric acid by GI bacteria together with inhibition of hepatic acetyl-CoA carboxylase.

must keep up with the increment in CO_2 production.

A decision needs to be made on the initial target P_{HCO3} when a patient has an extremely low baseline P_{HCO3}. A reasonable target is either to double the P_{HCO3} or to aim for an absolute value of 5 – 6 mM. If the P_{HCO3} rises from 2 to 4 mM and the PCO_2 remains unchanged, the pH will rise by 0.3 units. Nevertheless, one cannot make an accurate assessment of the amount of $NaHCO_3$ to give because the volume of distribution HCO_3^- is unknown.

Specific Causes for Metabolic Acidosis

The list of causes of metabolic acidosis is provided in Table 6.

Ketoacidosis

Ketoacids are a fat-derived fuel destined for oxidation in the brain. The main signal for their formation is a relative lack of insulin (Figure 3). There are 3 major causes of ketoacidosis (Table 12). In biochemical terms,

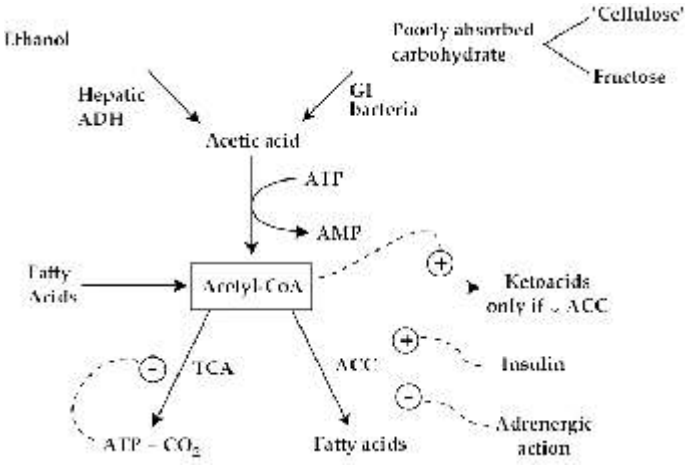

Figure 16. Metabolism of acetyl-CoA in the liver. There are two major sources of acetic acid and thereby hepatic acetyl-CoA, ethanol and acetic acid produced during the bacterial fermentation of poorly absorbed carbohydrates. Production of acetyl-CoA from these precursors bypasses the usual regulatory steps that involve fatty acid oxidation. Hence a high supply of these precursors and inhibition of acetyl-CoA carboxylase (ACC) by hormones such as adrenaline lead to the unregulated formation of ketoacids.

one must appreciate why there was a relative lack of insulin to favor ketoacid production and why the rate of removal of ketoacids was diminished. Production occurs in the liver whereas removal is largely the result of oxidation in the brain and kidneys (Table 11). The time course of events in patients with diabetic ketoacidosis (DKA) has an interesting feature. Towards the end-stage, the degree of ketoacidosis becomes more severe, and very quickly. Because there is little leverage to increase the rate of ketogenesis appreciably due to the control exerted by the limited rate of turnover of ATP in hepatocytes [85, 86], for ketoacidosis to worsen rapidly, there must be a major decline in the rate of utilization of ketoacids.

Brain: A decrease in the rate of turnover of ATP in the brain will lead to a decreased rate of oxidation of ketoacids. Should general anesthetics or sedatives be administered, or if coma be present, the degree of ketoacidosis will be more severe.

Kidney: If the GFR is very low, less Na^+ will be of filtered and this will decrease the reabsorption of Na^+ and thereby the renal need for regeneration of ATP. In quantitative terms, a low GFR can lead to the failure to remove several hundred mmoles of ketoacids per day.

Summary: One can appreciate why the natural history of DKA has a steep deterioration late in its course because of coma and prerenal failure.

Diabetic Ketoacidosis

DKA is the metabolic consequence of a lack of actions of insulin and it is characterized by the accumulation of glucose and ketoacids in the body [16]. The precipitating illness and the complications of this metabolic disturbance can be life-threatening. The changes in the hepatic metabolism that lead to overproduction of ketoacids are depicted in Figures 3 and 16.

Clinical Presentation

DKA may be the first indication of undiagnosed type 1 diabetes mellitus in children. The precipitating causes include an intercurrent illness (gastroenteritis, pancreatitis, infections), and situations where counter-regulatory hormones may be present in

excess (e.g., thyrotoxicosis, surgery, stress, pregnancy, and hyperadrenocorticism). With repeat episodes of DKA, failure to take insulin can be an important etiologic factor. Rarely, DKA occurs in older patients with type 2 diabetes mellitus when there is an unusually large decrease in the rate of oxidation of ketoacids due to impaired level of consciousness and a very low GFR.

The clinical manifestations are the expected consequences of the major biochemical changes, hyperglycemia, glucosuria, and ketoacidosis.

Hyperglycemia: Early signs and symptoms represent exacerbations of the classic features of diabetes mellitus in poor control – thirst, polydipsia, polyuria, weakness, lethargy, and malaise.

Glucosuria: Hyperglycemia causes an osmotic diuresis with loss of Na^+ and water, resulting in ECF volume contraction, low blood pressure, postural hypotension, and tachycardia.

Ketoacidosis: Metabolic acidosis results in an increased rate and depth of breathing (air hunger, Kussmaul respiration). The conversion of acetoacetic acid to acetone imparts the characteristic fruity odor to the breath.

Other findings: Not all the clinical findings, however, are completely explained in terms of biochemical aberrations. The state of consciousness does not correlate well with the concentration of ketoacids in blood. A much better correlation was found between the level of stupor and coma and the P_{osm} that in turn reflect the low circulating volume (and possibly, the higher PCO_2 in cells of the brain, Figure 7).

Another feature of DKA that remains unexplained is hypothermia, even in the presence of infection. This together with the fact that leukocytosis is a common finding in these patients may at times obscure an underlying infection.

Anorexia, nausea, vomiting, and abdominal pain are frequent nonspecific gastrointestinal complaints, especially in children. These symptoms, together with abdominal tenderness, decreased bowel sounds, guarding, and leukocytosis, may be severe, mimicking an acute abdominal emergency. Rebound tenderness is usually (but not universally) absent – the presence of hyperglycemia and ketonemia should signal the correct diagnosis. The cause for the abdominal pain is not entirely clear, but in some cases it may be related to hypertriglyceridemia and pancreatitis.

Signs and symptoms of the disorder that precipitated DKA should be appreciated – in fact, these may dominate the clinical picture.

Laboratory Evaluation

Hyperglycemia, ketonemia, glucosuria, and ketonuria are the 4 hallmarks of the laboratory diagnosis of DKA.

Hyperglycemia: The degree of hyperglycemia varies markedly – the P_{Glu} usually exceeds 250 mg/dl (14 mM). Higher P_{Glu} values are seen if there is a marked reduction in the GFR (usually with oliguria) or if the patient has consumed a large quantity of carbohydrate, for example, in the form of sweetened soft drinks to quench thirst (usually with polyuria) [87]. If the ECF volume is markedly contracted, not only will there be an exaggerated degree of hyperglycemia, but glucosuria may be reduced considerably because the filtered load of glucose may not exceed the tubular capacity for its reabsorption. In rare cases, hyperglycemia may be less marked for other reasons (e.g., a reduced rate of gluconeogenesis secondary to the intake of ethanol or biguanides or exaggerated renal glucosuria).

Ketoacids: In DKA, serum ketones are usually strongly positive in a dilution of 1 in

Table 13. Typical deficits in a patient with DKA.

	Quantity	Comment	Danger
Na^+	3 – 9 mmol/kg	Restore Na deficit, but not too quickly	Cerebral edema if early and too rapid
K^+	4 – 6 mmol/kg	Must await insulin action to shift K^+ into cells Examine P_K	Initial hyperkalemia > 1.5 h, hypokalemia
Water	Usually many liters	Half ICF, half ECF	Do not repair water deficit too early
Bicarbonate	Can be > 500 mmol of H^+ buffered	If increased anion gap, need not give $NaHCO_3$ unless very severe acidosis	Strong opinions held, but not backed up with clean data

8. However, only acetoacetate and acetone yield a positive reaction with the nitroprusside test (Acetest) used for clinical screening for ketoacids. If there is an increase in the $NADH^+$: NAD ratio, as occurs with hypoxia or ethanol oxidation, ketoacids will be predominantly in the form of -hydroxybutyric acid which is not detected by these clinical tests; a specific enzymatic analysis will be necessary to measure -hydroxybutyric acid. If the urinary excretion of ketoacid anions is larger than expected, as may occur with the intake of acetylsalicylic acid, or if there is a defect in reabsorption of ketoacid anions by the PCT, a hyperchloremic type of metabolic acidosis will be present [88].

Sodium: In patients with DKA, there is a large deficit of Na^+ (3 – 9 mmol/kg body weight, Table 13). This is the result of the osmotic diuresis.

Plasma Na^+ concentration: Much attention is given to the possibility that glucose will draw water out of cells and thereby, lower the P_{Na}. This occurs only when the addition of glucose is hyperosmolar to plasma. In contrast, when glucose is added as a solution that has an osmolality similar to or lower than the P_{osm}, there is no shift of water from cells. In this circumstance, the P_{Na} will be lower than seen with hypertonic glucose addition for an identical rise in P_{Glu} [89]. Therefore calculations based on the expected shift of water and thereby an expected fall in P_{Na} for a given P_{Glu} should not be done because the assumptions made are not valid [90 – 92]. Therefore we calculate the effective P_{osm} (Equation 10) to help clinical decision-making with regard to the appropriate tonicity of fluid therapy [93]. Corrections should be made for major changes in the P_K.

$$\text{Effective } P_{osm} = 2 \times P_{Na} + P_{Glu} \quad \text{(in mM terms)} \qquad (10)$$

Potassium: In patients with DKA and good renal function, there is always a decrease in the total body content of K^+, usually in the range of 4 – 6 mmol/kg body weight (Table 13). Despite this deficit of K^+, the P_K is usually increased to the mid-5 range [94] because K^+ has shifted from the ICF to the ECF

Table 14. Content of HCo_3^- in the ECF compartment in a patient with DKA. The example given is a 70-kg person who has an ECF volume of 15 L when normal (top line) and 12 L while in DKA (bottom line). The content of HCO_3^- is decreased by 75 mmol in DKA. Despite this loss, there is a 1:1 relationship between the fall in P_{HCO3} and rise in P_{-HB} because of an equivalent loss of -HB with Na^+ and/or K^+ in the urine. This represents the indirect loss of $NaHCO_3$.

	Plasma		ECF volume	ECF content		
	P_{HCO3} mmol/l	P_{-HB} mmol/l	liters	HCO_3^- mmol	Ketoacids mmol	$HC0_3^-$ + Ketoacids mmol
normal	25	0	15	375	0	375
DKA	10	15	12	120	180	300

compartment due to the lack of insulin (Figure 9) [73].

P_{HCO3}: In patients with DKA, the P_{HCO3} is low because H^+ were added to the ECF along with -hydroxybutyrate and acetoacetate anions. Nevertheless, there is also an indirect loss of Na^+ and HCO_3^- – this loss occurs early in the course of DKA because there is a lag period before there is a large increase in the rate of excretion of NH_4^+ [15]. As a result, ketoacid anions are excreted in the urine with Na^+ or K^+ and hence the indirect loss of $NaHCO_3$ (Figure 4). This component of the metabolic acidosis may not be appreciated because there is often a 1 : 1 relationship between the fall in P_{HCO3} and the rise in the plasma anion gap. This quantitative relationship occurs because *concentrations* rather than the *content* of HCO_3^- in the ECF compartment are considered (Table 14). This component of the HCO_3^- deficit becomes evident during therapy as the ECF volume is expanded [69, 95, 96].

PCO_2: There should also be a predictable degree of hypocapnia depending on the degree of metabolic acidosis (Table 4). Since hypothermia may occur in patients with DKA, one must take this into consideration when interpreting the PCO_2 and PO_2 values reported by the laboratory because the measurements are made at 37ºC.

GFR: Since patients with DKA often have a very low ECF volume, their GFR will be reduced whereas the concentrations of urea (P_{urea}) and creatinine (P_{creat}) will be elevated in plasma. The P_{urea} (BUN) is less reliable as an index of the GFR because it is also influenced by protein intake, tissue catabolism, rate of gluconeogenesis, catabolic drugs, and urine flow rate. Notwithstanding, there may also be errors in the measurement of creatinine depending on the method used. Higher P_{creat} values are reported with the picric acid method if the level of AcAc is elevated [97] whereas lower P_{creat} values are reported with severe hyperglycemia if the enzymatic assay for creatinine is performed on the Kodak analyzer [98].

Treatment of the Patient with DKA

DKA is a medical emergency that demands urgent treatment. Mortality is influenced by a number of factors that include its precipitating cause, the age of the patient, the level of

consciousness, and the severity of the biochemical abnormalities. In children, the leading cause of morbidity and mortality is the development of cerebral edema (discussed later) [99, 100]. Other causes of death are infection, vascular thrombosis, and shock. Early diagnosis, a better design of therapy, and dealing with the underlying causes of DKA may reduce the mortality rate. Our emphasis will be on the threats to the patient's life during therapy of DKA (Table 15). Treatment will be discussed under the following headings: body fluid compartments, insulin, bicarbonate, predisposing factors and how to avoid complications of therapy.

Table 15. Complications to avoid during therapy.

On admission
Shock
Aspiration pneumonitis
Thrombotic episodes
Hyperkalemia with cardiac arrhythmias
From 1.5 h onwards
Hypokalemia with cardiac arrhythmias
From 6 h onwards
Neuroglucopenia
From 5 – 15 h
Cerebral edema
Anytime
Complications of the underlying illness
Lack of insulin actions

Body Fluid Compartments

Focus on the ECF volume: The ECF volume should be re-expanded quickly only if there is a hemodynamic emergency. It is very difficult to assess the degree of ECF volume contraction on clinical grounds [101 – 103]. The following laboratory findings can help to provide a quantitative assessment of the patients' ECF volume [69]. The hematocrit (ratio of red blood cells (RBC) volume/blood volume) is particularly useful if the patient is not anemic. For example, if the initial hematocrit were 60%, this would suggest that the plasma volume is contracted by more than 50% (Equation 11). Moreover, the ECF volume is contracted to a greater degree than the plasma volume because the volume of RBC should remain constant (in the absence of a severely abnormal P_{Na}) and Starling forces should expand the plasma volume at the expense of the interstitial volume [69].

Normal: 0.40 = 2 l RBC volume/5 l blood volume (3 l plasma + 2 l RBC)

Patient: 0.60 = 2 l RBC volume/3.3 l blood volume (1.3 l plasma + 2 l RBC) (11)

We also find 2 other indices helpful to monitor changes in the effective vascular volume [69]. First, if the venous PCO_2 is appreciably higher than the arterial PCO_2 (> 10 mmHg), it suggests a slower blood flow rate past cells drained by that venous system (same CO_2 production, but CO_2 is carried away in fewer liters of blood, Figure 7). Second, a rise in urine output usually signals an increase in the GFR and thereby a higher filtered load of glucose and a larger osmotic diuresis. With the initial urine output rise, the rate of intravenous infusion should be increased by a similar volume to maintain the slow and steady re-expansion of the ECF volume.

The next decision concerns the composition of the infusate. There is still some dispute about which is the most appropriate intravenous solution to use. We strongly favor the initial administration of 0.9% saline (154 mM NaCl) to avoid a large fall in the effective P_{osm} (Equation 10). When the P_{Glu} falls below 250 mg/dl (15 mM), glucose should be added to the infusate. Further fluid therapy is determined by the clinical assessment, biochemical measurements, and calculated and/or expected losses.

Focus on the ICF volume: The deficit of ICF water should be replaced much more slowly. Once the hemodynamic emergency is dealt with, one can now safely switch to half isotonic saline in adults with DKA because cerebral edema is not common in these patients. The goals for ICF therapy differ in children with DKA as discussed later in the section on complications of therapy.

Insulin: Insulin plays a central role in arresting ketogenesis, but this is rarely an urgent aspect of therapy because the maximum possible rate of ketogenesis is only ~ 1 mmol/min [86]. In our view, the only emergency action of insulin needed is its effect to decrease the P_K by accelerating a shift of K^+ into cells in a patient with a significantly abnormal EKG due to hyperkalemia. While insulin will help lower the P_{Glu}, its hypoglycemic effects are minimal early in therapy. Rather, the P_{Glu} will fall initially as a result of re-expansion of the ECF volume (dilution) and glucosuria (decrease the glucose pool size) [104]. 6 – 8 hours after therapy began, insulin will increase the rate of oxidation of glucose (because competing fat fuels are no longer available) and by promoting the synthesis of glycogen [87].

Low-dose, short-acting insulin regimens are now commonly used. Given the uncertainty of absorption by other routes, the intravenous route is advisable. A typical dose in adults is 0.1 Units/kg as an intravenous bolus, followed by a constant infusion of 0.1 Units/kg/h. A bolus of insulin should not be used in children because it may lead to brain cell swelling [93]. The putative mechanism involves activation of the Na^+/H^+ exchanger in brain cell membrane with a resultant gain of ICF solutes (Na^+) [105].

Insulin therapy has potentially detrimental effects that should be anticipated and avoided. The major ones are hypokalemia (at 1 – 3 h) and hypoglycemia (at 6 – 10 h). The former risk is discussed below and the latter one is minimized by infusing glucose when the P_{Glu} falls to 250 mg/dl (~ 15 mM).

Potassium: Typically, the P_K on presentation in patients with DKA is in the mid-5 range [94]. A lower P_K indicates that a rather severe K^+ deficit exists and patients are at higher risk for cardiac arrhythmias, paralytic ileus, and muscle weakness that may also involve respiratory muscles after insulin is given. Once therapy has commenced, the P_K falls rapidly, often within the first hour. This is due primarily to the uptake of K^+ into the ICF (replacing Na^+ and H^+). Minor contributing factors are the loss of K^+ in the urine, correction of the acidosis, and dilution from re-expansion of the ECF volume.

The initial aim of therapy is to ensure a normal P_K during the acute stages of therapy. Replenishing the total deficit of K^+ in the body will take time because it requires the re-accumulation of intracellular anions (primarily organic phosphates). K^+ should be given as intravenous KCl, but only when the P_K is < 5.0 mM. Typical regimens are: give 20 mmol K^+/hour if the P_K is 4 – 5 mM; give 40 mmol K^+/hour if the P_K is 3.0 – 4.0 mM, and 40 – 60 mmol K^+/hour if the P_K is < 3.0 mM. The EKG as well as the P_K can be used to monitor the rate of replacement of K^+.

While it is prudent to consider the urine output, patients with oliguria may still need a supplement of K^+ if their P_K is distinctly low. When DKA has been corrected, oral supplementation of K^+ (and phosphate, usually from diet) should be continued over several days to replenish the deficits in the intracellular compartments.

Because hypokalemia is also a complication of therapy with $NaHCO_3$, if a patient presents with a low P_K and acidosis that is severe enough to require treatment with $NaHCO_3$, one could make a case for withholding insulin for an hour or so until suffi-

cient K^+ and HCO_3^- have been administered. Since the rate of net ketoacid production is ~ 1 mmol/min [86], withholding insulin for that hour will not have a major impact on the degree of acidosis because more HCO_3^- than this can be given.

$NaHCO_3$

Early therapy: $NaHCO_3$ is rarely needed. Nevertheless, it is difficult to resist giving $NaHCO_3$ when the P_{HCO3} is < 5 mM especially if there is a source of loss of $NaHCO_3^-$. A severe degree of hyperkalemia is also a possible indication for the use of $NaHCO_3$.

Later therapy: After the ketoacidosis has been largely reversed, some patients may have a lingering hyperchloremic type of metabolic acidosis due in part to a low rate of excretion of NH_4^+. These patients may need to ingest $NaHCO_3$ to raise their P_{HCO3}.

Phosphate

The usual deficit of phosphate is 1.5 – 2.5 mmol/kg body weight (Table 13). While only close to 10% of patients have hypophosphatemia at presentation, once therapy is instituted virtually every patient becomes profoundly hypophosphatemic. There are no controlled studies documenting the absolute benefits of the acute replacement of phosphate. A number of theoretical considerations, however, suggest that it may be beneficial to replace some of the deficit of phosphate early in therapy. The rate of infusion of phosphate should not exceed 50 mmol/8 h.

Complications Observed During Therapy

While hypokalemia, hypoglycemia, relapse of ketoacidosis, and thrombotic events may occur, we shall focus on cerebral edema in this section.

Cerebral edema: Typically, DKA is first diagnosed in childhood. Cerebral edema is more common during therapy in the first episode of DKA, possibly because there was a delay in suspecting that this may be the diagnosis by family members. Cerebral edema occurs in ~ 1% of cases and it is the major cause of mortality in this setting [99, 100]. Even though most children with cerebral edema survive, many are left with significant neurological deficits. Even those who seem to be neurologically intact may have subtle cognitive and behavioral deficits.

Cerebral edema is the result of a rise in brain water and hence intracranial pressure because of the fixed volume of the skull. At the clinical level, typically, the child who develops cerebral edema appears to be recovering normally from DKA, but takes a rapid turn for the worse close to 5 – 15 h after the onset of therapy. Nevertheless, 1/20 children developed cerebral edema prior to receiving therapy – a possible reason for this was discussed in reference [89]. The warning signs of impending cerebral edema are often subtle, including new onset of drowsiness and/or irritability that can progress rapidly to a disordered state of consciousness that may terminate with respiratory arrest and death.

While CT or MRI imaging will confirm this diagnosis, we are very reluctant to send patients suspected of having cerebral edema for these studies because they need extremely urgent medical treatment that cannot wait for even a few minutes. Moreover, they need to be observed very carefully and the imaging department does not have the facilities to do

Table 16. Anticipated results of therapy of DKA.

Glucose:	Will fall 5.5 mmol/l (100 mg/dl) over each of the first 6 hours. Reasons for fall are dilution (early), glucosuria (mid-time) and metabolism (late).
Sodium:	Rise in the P_{Na} of 1.6 mmol/l per 100 mg/dl (5.5 mmol/l) decline in P_{Glu} owing to a shift of water into the ECF.
Potassium:	Sudden fall over 1 – 2 hours owing to shift of K^+ into cells when insulin acts. This is the best early indicator of the biological actions of insulin.
Bicarbonate:	Will not rise for several hours. The P_{HCO3} will be close to 16 – 18 mmol/l once ketoacidosis largely disappears (6 – 8 hours later).
Ketoacids:	Slow steady decline over 8 hours to 1 mmol/l range. Serum quick test for ketones will be positive much longer. The Quick test may actually become more positive, despite less ketoacidosis owing to conversion of H● -HB to H●AcAc.
Anion gap:	Fall in parallel with ketoacids, will return to normal in 8 – 12 hours.
Complications:	See Table 15.

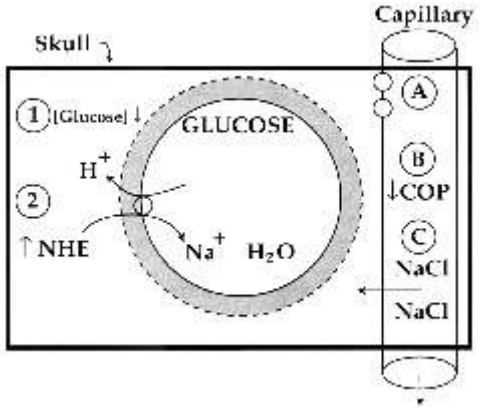

Figure 17. Risk factors for cerebral edema. The solid rectangle represents the skull. The 2 risk factors for swelling of brain cells are shown on the left and include a higher concentration of glucose and/or its metabolites in the brain due to rapid lowering of the P_{Glu} (site 1) and activation of the $Na^+ : H^+$ exchanger (NHE) by insulin (site 2). The factors causing expansion of the ECF volume are shown on the right and could be the result of a less restrictive blood brain barrier (site A), a fall in the colloid osmotic pressure (COP) in plasma (site B), and/or the excessive administration of saline (site C). Reproduced with permission [187].

this. Even when one has the results of the imaging studies, changes in the clinical state can occur so rapidly that this result may not mirror the current status in a timely fashion.

Pathophysiology of Cerebral Edema

A more detailed view of the pathophysiology of cerebral edema will be considered under the following headings (Figure 17).

Factors related to an expansion of the ECF compartment of the brain: One can think of these as early or later events. The early factors might include a less restrictive blood brain barrier (BBB), the use of an initial bolus of saline, especially if there is not a hemodynamic reason to give it, and an initial decline in the colloid osmotic pressure of plasma. In more detail, although somewhat controversial, there is evidence of subclinical cerebral edema before therapy is instituted when CT scans of the brain were examined [106 – 108]. This may be the result of a less restrictive BBB that permits the intracranial

ECF volume to increase, effectively bypassing the protective mechanisms that normally exist to prevent a rise in intracranial pressure. The initial bolus of saline will be distributed on first pass in the blood volume and cause a sudden rise in hydrostatic pressure and a fall in the colloid osmotic pressure of arterial blood. In addition to the fall in albumin concentration, the colloid osmotic pressure could decrease due to a fall in the Donnan force in plasma, possibly the result of a less anionic charge on albumin associated with rapid re-expansion of the ECF volume [109]. Hence Starling forces together with a less restrictive BBB could act in concert to expand the volume of the intracerebral ECF compartment further. The message we derive from these analyses is: a large bolus of saline should **not** be given unless there is frank hemodynamic collapse in children with DKA.

Factors associated with a rise in brain cell volume: There are two factors to consider, a fall in the effective P_{osm} and a rise in intracellular osmoles. Firts treatment regimens that have been associated with cerebral edema usually cause a significant fall in the effective P_{osm} (Equation 10). A rapid fall in the P_{Glu} may predispose to cerebral edema by allowing the shift of water into brain cells (a compartment with an osmolality that decreases less rapidly than the effective P_{osm}). As partial compensation for the high effective P_{osm} in a patient with DKA, the brain seems to accumulate osmoles such as sorbitol, fructose, taurine and glutamine that minimize the degree of water shift out of brain cells. Once the P_{osm} falls, however, these organic osmoles cannot be removed rapidly from brain cells and they will attract water, contributing to the development of cerebral edema [110]. Second, one should avoid an initial bolus of insulin because it may cause an increase in the number of particles in cells of the brain [105]. In more detail, insulin activates the Na^+-H^+ exchanger in the cell membrane (Figure 9). By causing an increase in the entry of Na^+ into brain cells along with the exit of H^+ that were bound to intracellular proteins, there will be a net increase in the number of particles in the ICF, and this will draw water into these cells.

The P_{Na} is typically much higher in children for a given degree of hyperglycemia (i.e., with a P_{Glu} of 50 mM (900 mg/dl), the P_{Na} is usually in the 125 – 130 mM range in adults [81, 104] but closer to 140 mM in children [93, 111]. We speculate that this could reflect the higher GFR early in type 1 diabetes mellitus leading to a higher rate of glucosuria for the same degree of hyperglycemia. Moreover, the $U_{Na} + U_K$ in this urine is close to $^1/_3 - ^1/_2$ isotonic saline (plus glucosuria). Hence there would be a larger excretion of electrolyte-free water in children.

Issues for Therapy

The best strategy is to prevent cerebral edema from developing. This can probably be achieved by avoiding therapies that will over-expand the ICF and ECF volumes of the brain. We would not administer a bolus of insulin to treat DKA in children. The initial saline infusion should be targeted to avoid circulatory collapse – we would not otherwise give a bolus of saline. Once the patient is hemodynamically stable, the Na^+ deficit should be replaced slowly, with an upper limit of 6 – 9 mmol/kg depending on the initial impression of the degree of ECF volume contraction (use the hematocrit if possible) [69].

In children, we use isotonic saline to avoid a fall in the effective P_{osm} (Equation 10). The target value for the P_{Na} in the first 5 – 15 hours is that which keeps a constant effective P_{osm}. Adding KCl, to isotonic saline is a good choice when the patient is undergoing a rapid

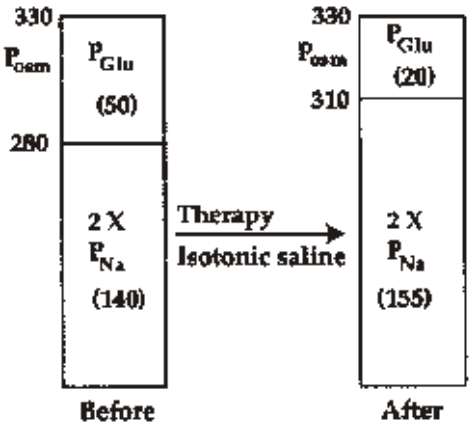

Figure 18. Fall in the effective plasma osmolality and the development of cerebral edema. For details, see text. A rise in the P_{Na} is needed to prevent a fall in the effective P_{osm} when there is a fall in the P_{Glu}. The P_{Na} must rise by $^1/_2$ the fall in the P_{Glu} to maintain a constant P_{osm} of 330 mOsm/kg H_2O.

glucose-induced osmotic diuresis because this will defend the effective P_{Osm} when the P_{Glu} falls. There is evidence to suggest that maintaining a constant "effective" P_{osm} at the expense of hypernatremia may protect against cerebral edema [93]. This can be accomplished by permitting the P_{Na} to rise by half the fall in P_{Glu} in mM terms (Equation 10), thereby keeping the effective P_{osm} constant (Figure 18). As mentioned earlier, the P_{Na} in children with DKA who have a P_{Glu} of 50 mM (900 mg/dl) is usually close to 140 mM [93, 111]. When this P_{Glu} falls by 30 mM (540 mg/dl), the P_{Na} would have to rise by 15 mM to 155 mM to keep the effective P_{osm} constant (Equation 10). To achieve this aim, the intravenous solutions must have the same effective osmolality as the P_{osm} in an oliguric patient or as the urine when the patient has a large urine output.

If signs of cerebral edema did develop, hypertonic saline or mannitol should be infused rapidly to reverse cerebral edema by drawing water out of the brain [112]. Our aim would be to give enough hypertonic solutes to see a prompt clinical response. Usually, this would require an increase in the effective P_{osm} of 10 mOsm/kg H_2O (administer 10 mmol of mannitol or 5 mmol of hypertonic NaCl/l body water using the clinical response as your guide).

Precipitating Events

During therapy for DKA, it is also necessary to treat any precipitating event or accompanying illness. Although clinical rhabdomyolysis is uncommon, enzymes of muscle origin (CPK, AST, and LDH) are often elevated in plasma. Thrombotic events in veins due to a slow blood flow rate should also be anticipated.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis is seen following binge drinking of large amounts of ethanol complicated by poor food intake and vomiting (usually due to alcohol-induced gastritis) [113, 114]. The lack of food intake and the ECF volume depletion lead to suppression of insulin secretion via an -adrenergic effect [115]. This combination of hormonal changes both increases lipolysis in adipose tissue (stimulation of hormone-sensitive lipase) and diminishes hepatic lipogenesis (inhibition of hepatic acetyl-CoA carboxylase (ACC)) (Figure 16).

Ethanol, the principal carbon source for the formation of ketoacids, is metabolized in the liver to produce acetyl-CoA. Constraints set by the rate of turnover of ATP in hepatocytes limits the rate of oxidation of acetyl-CoA to

produce ATP [85, 86]. This, together with the inhibition of the synthesis of fatty acids in liver (inhibition of ACC by the low insulin and high circulating counter-insulin hormones such as adrenaline and glucagon), leads to the rapid formation of ketoacids. The acidosis may be quite severe and have a relatively rapid onset, with ketoacid anion levels of up to 20 mM; it is associated with an increase in the anion gap in plasma. Establishing the diagnosis of alcoholic ketoacidosis may not be straightforward. One reason is that there are frequently coexisting acid-base disturbances that result in the blood pH being normal or even alkalemic in up to 50% of patients. Metabolic alkalosis commonly occurs as a result of the vomiting, and respiratory alkalosis may occur due to stimulation of ventilation by alcohol withdrawal or aspiration pneumonia.

The second difficulty in diagnosis is that there is occasionally a falsely low or perhaps negative screening test for ketones [116]. The nitroprusside reagent reacts with acetoacetate and acetone. Acetoacetate is in equilibrium with -HB in a reaction catalyzed by the enzyme -hydroxybutyrate dehydrogenase (Equation 12). This is an NAD^+-NADH linked reaction and the ratio of end products depends on the NAD^+/NADH ratio which in turn reflects the redox state in liver cells. In alcoholic ketoacidosis, the NAD^+/NADH ratio in the liver is often more reduced than usual due in part to the metabolism of ethanol (which generates NADH) or to tissue hypoperfusion as a result of the marked degree of ECF volume contraction. In this setting, the more reduced NAD^+/NADH ratio increases the amount of -hydroxybutyrate relative to that of acetoacetate so that the screening test for ketones may be falsely low.

$$AcAc^- + NADH + H^+ \qquad -HB^- + NAD^+ \quad (12)$$

The diagnosis of alcoholic ketoacidosis is therefore suspected in light of the clinical situation and laboratory abnormalities noted above. A key finding is that the P_{Glu} is not very elevated as it would be in DKA. At times it is difficult to distinguish alcoholic ketoacidosis from methanol or ethylene glycol poisoning as the primary cause of acidosis. This diagnosis is very important to make because therapy differs. Both can cause metabolic acidosis, a high anion gap in plasma, an elevated value for the plasma osmolal gap, and a near-normal P_{Glu}. Nevertheless, there is one clinical clue that can help – if the ECF volume is not very contracted, one would suspect methanol or ethylene glycol overdose. A direct assay for methanol and ethylene glycol is needed to establish the diagnosis.

Treatment of Alcoholic Ketoacidosis

The treatment of alcoholic ketoacidosis is usually straightforward. Isotonic saline is required to correct the marked degree of ECF volume depletion [113]; if the P_{Glu} is definitely low, a small quantity of glucose should be added to raise the P_{Glu} to the high-normal range. The higher P_{Glu} should now stimulate insulin secretion and thereby, diminish the rate of ketoacid production. Attention must be paid both to K^+ and phosphate depletion, which are common in this disorder. Treatment with $NaHCO_3$ is rarely required because the degree of acidemia is usually mild and the net production of ketoacids can be reversed quickly with appropriate intravenous fluid therapy. One must bear in mind that a deficiency of thiamin might be present in a patient who is malnourished so this vitamin must be given with the initial therapy in this setting.

The prognosis is usually excellent; in one case series only about 50% of the patients required hospital admission, and the mortality

Table 17. Causes of L-lactic acidosis.

Type A (hypoxic)
- circulatory failure (cardiogenic shock or secondary to sepsis)
- severe hypoxemia (lung problem or high altitude)
- severe anemia
- excessive demand for oxygen (e.g. generalized seizure, vigorous exercise)

Type B (compromised metabolism of L-lactate)
- a variety of diseases that severely affect the liver
- inhibition of gluconeogenesis (e.g. by ethanol)
- inborn error of metabolism affecting pyruvate dehydrogenase, the tricarboxylic acid
- cycle, or the electron transport system
- thiamine deficiency
- riboflavin deficiency or low bioactivity
- isoniazide (vitamin B_6 deficiency)

rate was only 1% including problems related to underlying lesions such as pneumonia and pancreatitis [114].

Ketoacidosis of Prolonged Fasting

Ketoacidosis of fasting is usually a mild disorder with a P_{HCO3} that is characteristically close to 18 mM and an anion gap that is less than 19 mEq/l (suggesting that the accumulation of ketoacid anions is not more than 7 mM). The rate of production of ketoacids is close to that in DKA, but the rate of production is matched by the removal of ketoacids by oxidation in the brain and kidneys plus their excretion with NH_4^+ in the urine [46]. The P_{Glu} is usually close to 60 mg/dl (3 mM). Specific treatment for this form of ketoacidosis other than re-feeding is not required because it is rapidly cured by intake of carbohydrate.

L-lactic Acidosis

L-Lactic acidosis may be classified into two major categories depending on whether or not the supply of oxygen is matched to tissue demands for energy metabolism. In type A L-lactic acidosis, the production of L-lactic acid is increased and its removal impaired because of tissue hypoxia (Figure 19). In contrast, in type B L-lactic acidosis, hepatic removal of L-lactate is impaired for reasons other than hypoxia [117] (Table 17).

Type A Lactic Acidosis

Type A L-lactic acidosis is particularly frustrating to treat because its underlying cause

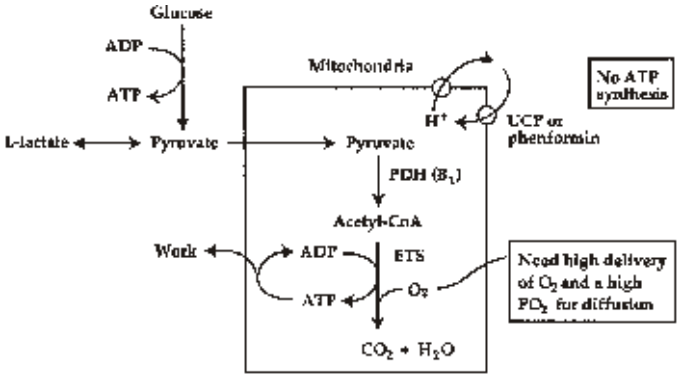

Figure 19. Biochemistry of L-lactic acidosis. The major production of L-lactic acid occurs when the supply of O_2 is inadequate to meet demand to support metabolic and physical work and/or uncoupling of oxidative phosphorylation due to open H^+ channels (UCP). Vitamin B_1 (thiamin), is a cofactor in the reaction catalyzed by pyruvate dehydrogenase (PDH). L-lactic acid can also accumulate when the ability to metabolize L-lactate is compromised.

may be extremely difficult to reverse. Examples include cardiogenic shock, septic shock, and multiple organ failure. It is also important to recognize that the rate of net L-lactate production may be extremely rapid, resulting in severe acidosis very quickly. It is widely believed that the accumulation of the L-lactate anion per se is not harmful and is important only as a sign of serious metabolic dysfunctions. Nevertheless, the L-lactate anion can chelate ionized Ca^{2+} [118 – 120], an ion that is critical for myocardial contraction [121]. In addition, Veech and Fowler [122] have suggested that a higher $NADH/NAD^+$ ratio can impair metabolism. Therefore there are theoretical reasons to suspect a primary role for the L-lactate anion in the poor outcome.

Hypovolemic shock: L-lactic acidosis caused by hemorrhage or extensive loss of Na^+-rich fluid (diarrhea, etc.) is the easiest of the causes to treat. Infusion of isotonic saline is the most appropriate initial therapy for most patients. In patients with severe hypoalbuminemia, colloids, such as albumin or plasma, may also be given. Whether one should add $NaHCO_3$ to the initial intravenous fluid depends on the factors discussed earlier – the severity of the acidosis, the respiratory compensation, the P_K, and probably most important, the likelihood of rapid reversal of the underlying cause of the hypovolemia. Usually, correction of hypovolemia will correct tissue hypoxia and rapid reversal of the L-lactic acidosis due to metabolic conversion of the accumulated L-lactate anions to HCO_3^- should be anticipated (~ 4 – 8 mmol of L-lactate may be removed per minute via oxidation or gluconeogenesis [2]).

Cardiogenic shock: This is much more difficult to manage, because the underlying cause of the tissue hypoxia – low cardiac output – is often difficult to reverse rapidly. Key issues to consider in patients with this diagnosis are ensuring that left ventricular filling pressure is adequate (which usually requires pulmonary capillary wedge pressure measurement) and that readily treatable causes of cardiogenic shock such as pericardial tamponade are not overlooked. The use of inotropes, afterload reducing agents, and/or an intraaortic balloon pump may be required. The administration of $NaHCO_3$ is often of limited use because of constraints imposed by ECF volume expansion and pulmonary edema.

Septic shock: L-lactic acidosis in a patient with sepsis is a grave prognostic finding. Treatment of the underlying infection with appropriate antibiotics, surgical drainage of an abscess if present, optimization of intravascular volume, and the use of inotropic agents are all essential, but often futile once multiple organ failure is present.

Use of dichloroacetate: One approach to treatment of patients with L-lactic acidosis is to use dichloroacetate (DCA) [123]. DCA activates the pyruvate PDH and thereby facilitates pyruvate (and therefore L-lactate) removal via metabolic conversion to acetyl-CoA and then to CO_2 and water. This may allow for more regeneration of ATP per molecular of O_2 consumed because now glucose or L-lactate rather than fatty acids are selected as the fuel to be oxidized [124]. DCA may have beneficial effects on myocardial function via a similar mechanism.

Early reports on the use of DCA in critically ill patients with L-lactic acidosis were somewhat encouraging. Notwithstanding, a prospective, randomized controlled trial of 252 patients with L-lactic acidosis, the majority of whom had sepsis and multi-organ failure, failed to show clinically significant benefit of DCA [125]. The results are not surprising considering that 18 mmol of H^+ are produced when 18 mmol of ATP are regenerated by anaerobic glycolysis, but only 1 mmol of H^+ is removed when the same amount of ATP is re-

generated by the aerobic oxidation of L-lactate [2]. Therefore one cannot overcome a rapid rate of production of L-lactic acid by enhancing its rate of removal unless anaerobic glycolysis is inhibited. Furthermore, as pointed out before, L-lactic acidosis per se maybe an epiphenomenon that reflects the presence of serious metabolic dysfunctions.

Type B L-lactic Acidosis

Hepatic disease: L-lactic acidosis is frequently seen in patients with acute hepatic necrosis with liver failure, such as that caused by viral hepatitis. It may also be seen as a more stable, chronic L-lactic acidosis where L-lactate removal is impaired in patients, for example, with malignancy that have liver metastases or infiltration with or without a large tumor burden outside the liver. The mechanisms that contribute to the L-lactic acidosis in these patients include replacement of a sufficient number of liver cells with tumor cells to impair L-lactate removal, production of metabolites by tumor cells such as the amino acid tryptophan that may lead to inhibition of hepatic gluconeogenesis, and/or the fact that tumor cells produce a quantity of L-lactic acid that exceeds the hepatic capacity to remove it in this setting.

Administration of $NaHCO_3$ to patients with type B L-lactic acidosis due to liver disease may have negative effects. First, the $NaHCO_3$ may increase L-lactate production (from glucose) by de-inhibiting phosphofructokinase-1 in malignant cells. Thus if the source of this glucose is ultimately from gluconeogenesis, a considerable amount of lean body mass may be lost [126]. Second, if for instance 150 mmol of $NaHCO_3$ were given along with 1 l of D_5W, the 276 mmol of glucose provided could be converted to 552 mmol of H^+ (2 L-lactate- and 2 H^+ per glucose), a quantity that exceeds the 150 mmol of HCO_3^- given.

Thiamin deficiency: Thiamin (vitamin B_1) deficiency is a specific example of type B L-lactic acidosis that merits emphasis. Thiamin is an essential cofactor of the PDH complex, an enzyme required for the regeneration of ATP from glucose [2, 127]. A special circumstance where the effect of thiamin deficiency can be very acute occurs when ketoacids were the main brain fuel (alcoholic ketoacidosis), but ketoacids disappeared when insulin levels rise (restoration of ECF volume, especially if hyperglycemia is also present). The target organ for a deficit of thiamin is the brain for two reasons: first, the brain is dependent on glucose as its energy fuel, and therefore flux through the PDH must occur in order to have ATP regeneration (unless ketoacids are present); second, there are very high rates of ATP turnover in certain areas of the brain. Hence, one can anticipate two hazards from a deficiency of thiamin, a local deficit of ATP, and a consequent local H^+ accumulation in an organ with limited buffer capacity. This may help explain why Wernicke-Korsakoff syndrome develops in these patients. Treatment is obviously thiamin replacement *before* the ketoacid concentration in plasma falls to very low levels.

Thiamin deficiency is most often seen in alcoholics who are poorly nourished, but it has also been described in patients receiving total parenteral nutrition when thiamin was not supplemented. The clinical manifestations of the L-lactic acidosis due to thiamin deficiency are confusion, hypotension, tachycardia, tachypnea and signs of congestive heart failure.

Ethanol: The acidosis observed in patients who have consumed large quantities of ethanol is frequently multifactorial. One component that may be observed in addition to ketoacidosis is L-lactic acidosis. The degree

of L-lactic acidosis is usually mild (< 5 mM) because it reflects the more reduced $NADH/NAD^+$ ratio due to ethanol metabolism that is largely restricted to the liver. A more severe degree of L-lactic acidosis suggests that there is L-lactic acid overproduction caused by hypoxia (resulting from shock due to gastrointestinal bleeding, for example), thiamin deficiency, seizures (alcohol withdrawal, delirium tremens, and/or a CNS lesion), or L-lactic acid underutilization due to severe liver disease. The management of this situation is mainly supportive, including normalization of the ECF volume and provision of thiamin. Once ethanol is completely metabolized, NADH levels will fall, L-lactate will be converted to pyruvate, and thereby to either glucose and/or CO_2 and water. This will lead to the regeneration of HCO_3^-, and the resolution of the L-lactic acidosis.

Biguanides: Biguanides are frequently used for patients with type 2 diabetes to lower the P_{Glu}. Initially, phenformin was the drug that was used, but because it led to the development of L-lactic acidosis [128], its use was curtailed. Currently, metformin is the drug of choice in this class – it does not seem to be a single cause of L-lactic acidosis [128b]. Biguanides, are lipophylic weak acids that can cross the mitochondrial membranes and cause uncoupling of oxidative phosphorylation in a fashion similar to dinitrophenol. The reason for the higher likelihood of L-lactic acidosis with phenformin than metformin is that phenformin has a larger hydrophobic end. Certain conditions lead to higher blood levels of these drugs, including renal insufficiency, reduced liver function or alcohol abuse, and heart failure and therefore, patients with these conditions are more predisposed to serious L-lactic acidosis with this class of drugs.

Antiretroviral drugs: L-lactic acidosis has been reported in patients with HIV infection treated with various antiretroviral agents. The agent most frequently associated with L-lactic acidosis is zidovudine [129], but didanosine, stavudine, lamivudine, and indinavir have also been implicated. Antiretroviral drug therapy is associated with mitochondrial myopathy as well as hepatic steatosis. Either muscle or liver involvement could, in theory, explain the L-lactic acidosis. Initially, mitochondrial myopathy, as manifested by ragged-red fibers and mitochondrial DNA depletion, was thought to be the main mechanism of L-lactic acidosis. Because the L-lactic acidosis did not become much more severe with exercise [129], we suspect that a more likely mechanism of the lactic acidosis might be the massive hepatomegaly and steatosis (Figure 20). This view was supported by the fact that a small dose of ethanol markedly increased the degree of L-lactic acidosis [129].

Riboflavin deficiency and/or tricyclic antidepressants: The active metabolites formed from vitamin B_2 (riboflavin), flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), are components of the mitochondrial electron transport system, the principal pathway to regenerate ATP, and for the enzyme, glutathione reductance. Riboflavin must be activated via an ATP-dependent kinase to produce FMN and FAD (Figure 21). This kinase is inhibited by tricyclic antidepressant drugs, such as amitriptyline and imipramine [130]. The activity of the kinase is decreased in hypothyroidism. Decreased activity of this kinase in a patient with myxedema crisis was associated with pyroglutamic acidosis [131]. Patients who consume a diet that is poor in B vitamins and take this class of antidepressants, can develop a chronic form of L-lactic acidosis. The reason that this is a chronic steady state L-lactic acidosis is still not clear.

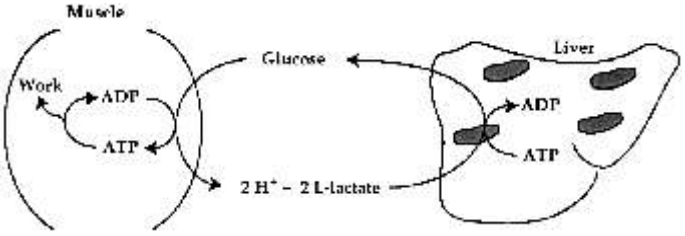

Figure 20. L-lactic acidosis and anti-retroviral drugs. The major basis for L-lactic acidosis is due to a problemwith L-lactic metabolism in the liver. While a lower activity of the mitochondrial electron transport system is possible, we favor the hypothesis that a large replacement of liver parenchyma by triglyderides (hepatic steatosis, depicted by the gray ovals) could explain why there is a reduced rate of L-lactic acid removal and a sensitivity to ethanol-induced L-lacitc acidosis.

The diagnosis is suspected by the history, and riboflavin deficiency is supported by finding a low activity of glutathione reductase in erythrocytes (a flavoprotein-dependent enzyme). Riboflavin supplementation leads to a prompt reversal of the metabolic acidosis in these patients suggesting that the defect is via competitive inhibition that is overcome by high riboflavin levels [132, 133].

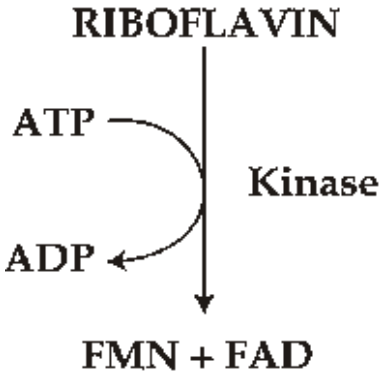

Figure 21. L-lactic acidosis and riboflavin deficiency. Riboflavin (vitamin B_2) must be activated to FMN or FAD to become an active component in the electron transport system, the mitochondrial pathway to regenerate ATP. Either a deficiency of riboflavin or inhibition of its kinase by tricyclic antidepressant drugs can lead to low levels of FMN and/or FAD.

Isoniazide: Prolonged convulsive seizure, regardless of cause, can lead to L-lactic acidosis. The seizure disorder induced by isoniazide is interesting because of its mechanism and clinical importance (Figure 22). Of note, the incidence of tuberculosis is rising worldwide and isoniazide is frequently used for its therapy.

The mechanism of the seizure and L-lactic acidosis may be the result of the formation of an isoniazide-vitamin B_6 complex, pyridoxal--isonicotinoyl-hydrazone, via a non-enzymatic reaction. This results in a rapid development of vitamin B_6 (pyridoxine) deficiency state [134]. Pyridoxal phosphate is a cofactor for the enzymatic reaction of glutamic acid decarboxylase in which glutamate is converted to gamma amino butyric acid (GABA). GABA is an inhibitory neurotransmitter. Therefore a deficiency of GABA could result in increased excitability and thereby lead to a seizure [135].

Patients on chronic hemodialysis are at increased risk of isoniazide-induced toxicity because they tend to be deficient in vitamin B_6 due to the efficient removal of this vitamin by hemodialysis. Vitamin B_6 deficiency can be suspected by finding a low activity of alanine aminotransferase in erythrocytes.

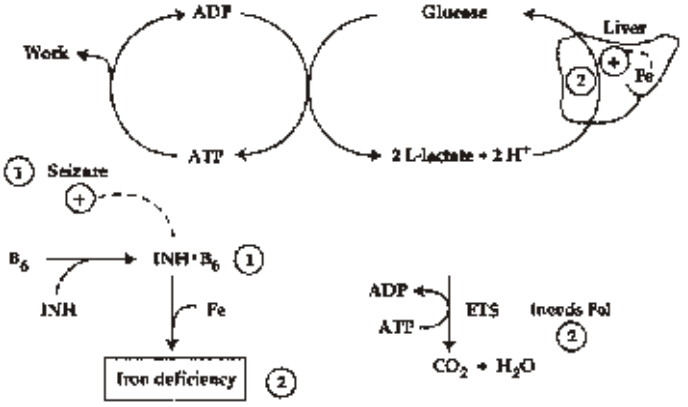

Figure 22. L-lactic acidosis due to the metabolism of isoniazide. For details, see text. The major cause of L-lactic acidosis is a seizure due to vitamin B_6 deficiency (site 1). A minor contributor to the development of lactic acidosis could be the chelation of iron (site 2) that diminishes the L-lactic acid removal rate, ETS electron transport system.

There are two factors that contribute to the degree of L-lactic acidosis (Figure 22). First, the deficiency of vitamin B_6 is responsible for isoniazide-associated seizure and thereby L-lactic acidosis. This is supported by the fact that there is a rapid and almost invariable cessation of seizure and recovery from L-lactic acidosis in response to a large dose of intravenous vitamin B_6 [136 – 138]. The recommended dose of vitamin B_6 for treatment of isoniazide toxicity is the same gram amount as the isoniazide dose ingested. If the amount of isoniazide is unknown, the recommended approach is to give 5 g of pyridoxine in 500 ml of fluid over 2 hours [138]. The second factor that could contribute to the degree of L-lactic acidosis is iron deficiency caused by chelation of iron by the isoniazide-vitamin B_6 complex. This could result in an electron transport defect and hence higher production of L-lactic and also a slower rate of its removal via gluconeogenesis because of the need for iron as a cofactor in both processes.

Methanol Poisoning

Methanol is metabolized by hepatic alcohol dehydrogenase. It is, however, a poor substrate for this enzyme and therefore high levels of methanol are needed for an appreciable rate of methanol metabolism. The molecular weight of methanol is only 32, so subjects do not need to ingest a large number of grams of methanol to produce an appreciable quantity of toxic metabolites. One can suspect that methanol is present from the history and the laboratory findings of a large plasma osmolal gap or metabolic acidosis accompanied by a large increase in the anion gap in plasma [139]. Note that the osmolal gap in plasma is due to methanol whereas the anion gap in plasma is due to formate anions. Therefore, later in the disorder when methanol has been largely oxidized, the plasma osmolal gap will not be elevated, but a high anion gap type of metabolic acidosis may be present.

The consequences of methanol ingestion may be classified as those arising from the effects of methanol itself and those of its metabolites. Methanol causes inebriation like ethanol. The serious toxicity of methanol arises from its metabolism to yield formaldehyde. Further metabolism of formaldehyde yields formic acid; however, acidosis is not usually the major concern. Formaldehyde is highly toxic to the central nervous system resulting in progressive coma and thalamic hemorrhage. The enzyme retinol dehydrogenase is located in the retina and it can catalyze the

conversion of methanol to formaldehyde and this leads to optic neuritis and blindness.

There may be difficulties in diagnosing methanol poisoning. In many cases, the origin of the ingested methanol is not recognized (e.g., substitution of methanol for ethanol in a recreational setting), so that clinical suspicion of the diagnosis may be lacking. Because methanol has such a low affinity for alcohol dehydrogenase, methanol toxicity can be delayed if ethanol is also ingested. Consequently, if one relies on finding metabolic acidosis, the diagnosis may be missed early on, even though plasma methanol levels are high. Accordingly, if there is the slightest suspicion that methanol may have been consumed and the plasma osmolal gap is significantly elevated, specific assays in blood for methanol should be undertaken. Another clue is that metabolic acidosis is present when the ECF volume is not appreciably contracted.

Treatment of Methanol Poisoning

First and foremost, the rate of metabolism of methanol to toxic end products should be slowed by giving ethanol or an inhibitor of alcohol dehydrogenase, 4-methylpyrazole (fomepizole, Antizol). The methods for administering Antizol and ethanol are described in the section on ethylene glycol.

Prognosis: The prognosis in methanol poisoning is closely related to the pH at presentation, with almost 100% mortality seen when the pH is less than 6.80. It is likely that the mortality is not caused directly by acidemia itself, but that the severity of acidosis reflects the generation of formaldehyde that causes the central nervous system toxicity. Therefore, although acidosis should be aggressively treated, the removal of methanol and its metabolites is the key to successful treatment.

Ethylene Glycol Poisoning

Ethylene glycol (automobile antifreeze, molecular weight 62) is readily available and is highly toxic. Like methanol, ethylene glycol is metabolized by the liver alcohol dehydrogenase to a variety of toxic end products. Patients with ethylene glycol poisoning have similar findings to those with methanol poisoning – CNS depression, increased anion gap metabolic acidosis and increased plasma osmolar gap. They differ in that they will often develop acute renal failure and pulmonary edema. The diagnosis may be suspected with the above findings plus abundant oxalate crystals in the urine, and confirmed by an assay that quantitates ethylene glycol in blood.

Treatment of Methanol and Ethylene Glycol Poisoning

The principles of treatment of ethylene glycol poisoning are virtually identical to that for methanol. They include administration of ethanol to achieve blood concentrations of about 20 mM (100 mg/dl) in order to reduce ethylene glycol metabolism, and removal of ethylene glycol and its metabolites by hemodialysis. One could administer fomepizole, an inhibitor of hepatic alcohol dehydrogenase, instead of ethanol. The major difference in treating ethylene glycol poisoning is that when acute oliguric renal failure is present, ECF volume overload or pulmonary edema may limit the amount of $NaHCO_3$ that can be administered so early dialysis is critically important.

Ethanol administration: Maintenance of a plasma ethanol level of about 20 mM (100 mg/dl) nearly completely inhibits methanol and ethylene glycol metabolism. Since ethanol distributes throughout total body water, administer a bolus of 0.6 g of ethanol per kg of body weight to increase its plasma level by 1

mg/ml (100 mg/dl). The maintenance dose should be equal to the expected metabolic removal rate for ethanol; at a plasma level in excess of 3 mM (14 mg/dl) – the hourly amount of ethanol removal is about 0.11 g per kg body weight [140]. In an alcoholic patient, the amount of ethanol metabolized is expected to be about 50% higher, and hence about 0.16 g of ethanol per kg body weight should be infused hourly. In a patient on hemodialysis, one can increase the rate of infusion of ethanol or add ethanol to the dialysis bath to achieve a concentration of 20 mM. The only way to ensure an optimal ethanol plasma level is to measure ethanol levels frequently and adjust its rate of infusion.

Administration of fomepizole (4-methylpyrazole): The target level of fomepizole in humans is 100 – 300 mol/l (8.6 – 24.6 mg/l) to assure near-complete inhibition of hepatic alcohol dehydrogenase. Its plasma half-life varies with the dose, even in patients with normal renal function. Fomepizole distributes rapidly in total body water. With multiple doses, fomepizole augments its own metabolism by inducing the cytochrome P450 mixed-function oxidase system; this effect increases the elimination rate by about 50% after about 30 – 40 hours. The side effects of fomepizole include headache, nausea, dizziness, and allergic reactions (rash and eosinophilia). Venous irritation and phlebosclerosis occur if the drug given is undiluted; therefore it should be diluted with at least 100 ml of 0.9% sodium chloride or D_5W.

The loading dose is 15 mg/kg, followed by 10 mg/kg q2h for four doses, then 15 mg/kg q12h (because of the P-450 enzyme induction) thereafter until the toxic alcohol level is less than 20 mg/dl. All doses should be administered as a slow intravenous infusion over 30 minutes. Fomepizole is dialyzable and the frequency of dosing should be increased to q4h during hemodialysis.

Salicylate Intoxication

The most common acid-base disturbance associated with salicylate intoxication is respiratory alkalosis due to central respiratory stimulation [141]. Metabolic acidosis may complicate the picture, however, especially in children. Because toxic levels of salicylate are considerably less than 10 mM (140 mg/dl), the elevation of the plasma anion gap in salicylate-associated metabolic acidosis is caused by the accumulation -HB, sometimes L-lactate anions, and other unidentified organic anions in addition to a small contribution by salicylates. Acidemia is uncommon because of coexisting respiratory alkalosis.

Treatment of Salicylate Intoxication

Treatment of salicylate intoxication is aimed at increasing urine salicylate excretion and preventing the accumulation of salicylates in brain cells. Salicylate is a weak organic acid that is transported across cells and renal epithelia, in its undissociated form. Alkalinizing the urine reduces salicylate reabsorption by the kidney and this may enhance its excretion; similarly, alkalinizing the ECF tends to prevent salicylate accumulation in cells, so acidemia should be avoided.

Alkalinizing the urine can be achieved with $NaHCO_3$ administration. The major risk of this therapy is excessive elevation of blood pH because of coexistent respiratory alkalosis and the risk of worsening pulmonary or cerebral edema. If the blood pH exceeds 7.55 as a result of this therapy, one dose of acetazolamide (250 mg) should be given to induce bicarbonaturia. Although acetazolamide causes an acid disequilibrium pH in the lumen of the PCT, it still promotes salicylate excretion [142]. One must avoid larger doses of acetazolamide as this may induce significant meta-

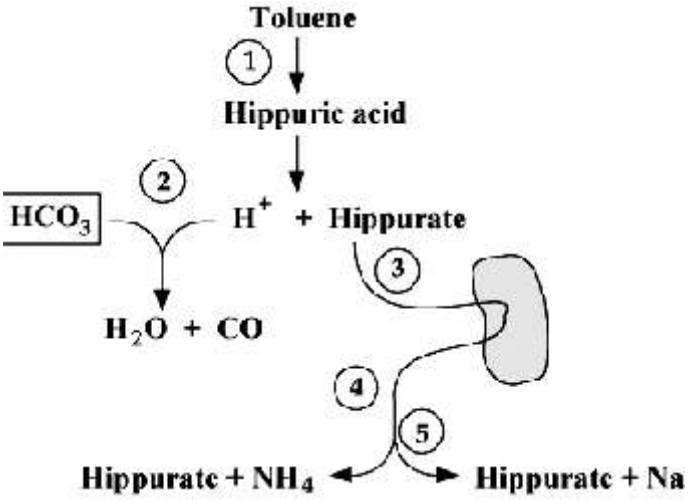

Figure 23. Metabolic acidosis due to the metabolism of toluene. The metabolism of toluene occurs in the liver. It is initiated by cytochrome P450, and then benzoic acid is produced via alcohol and aldehyde dehydrogenases. Hippuric acid is produced due to conjugation with glycine (all represented as site 1 for simplicity). The H^+ are titrated by HCO_3^- for the most part (site 2). The hippurate anion is secreted by the PCT and excreted in the urine, initially with NH_4^+ (site 4) and then with Na^+ and K^+ when the capacity to excrete NH_4^+ is exceeded (site 5). The excretion of hippurate anions with Na^+ and/or K^+ (and not NH_4^+) is the main reason for the metabolic acidosis.

bolic acidosis. Of more importance, acetazolamide will bind to albumin and displace bound salicylates thereby increasing its toxicity [143]. Acetazolamide also causes excessive losses of K^+ in the urine due to inducing bicarbonaturia.

In severe intoxications complicated by the adult respiratory distress syndrome, cardiovascular instability, evidence of cerebral edema, and possibly with severe elevations in salicylate level per se (greater than 6 mM), hemodialysis is the treatment of choice; if hemodialysis is not available, peritoneal dialsis may be used.

Metabolic Acidosis due to Glue-sniffing

Patients who sniff glue for its intoxicating properties absorb a significant quantity of toluene (methylbenzene). Toluene is metabolized via a series of reactions in the liver to hippuric acid that provides the load of H^+ (Figure 23). Despite the production of the hippurate anion, the plasma anion gap is generally not significantly elevated because the kidney, both via filtration and more importantly by tubular secretion, very efficiently excretes hippurate. As a result, there is the development of a hyperchloremic type of metabolic acidosis. Together with the anion excretion, variable amounts of urinary excretion of Na^+ and K^+ may be seen, leading to a degree of ECF volume contraction and hypokalemia, both of which aggravate the degree of intracellular acidosis (Figure 7). Even though there is an enhanced rate of excretion of NH_4^+, this does not result in a negative urine net charge (i.e., $U_{Na+K} > U_{Cl}$, Figure 11) because of the very high rate of excretion of the hippurate anion. The presence of NH_4^+ and hippurate in the urine could be detected by the presence of a significant urine osmolal gap (Figure 11). Thus the clinical features of toluene intoxication include metabolic acidosis, near-normal plasma anion gap, normal plasma osmolal gap, ECF volume contraction, hypokalemia, lower than expected BUN and

a high urine osmolal gap. It had formerly been thought that glue-sniffing was a cause of distal RTA [144], but the high rate of excretion of NH_4^+ in response to the metabolic acidosis in many of these patients means that they do not have distal RTA. Some patients may have another reason for a low rate of excretion of NH_4^+ (e.g., a low GFR) so they have two reasons for the metabolic acidosis, excessive overproduction of hippuric acid and a low rate of NH_4^+ excretion. If the GFR is low enough, there may now be a high anion gap in plasma [21].

Treatment of Metabolic Acidosis due to Glue-sniffing

The treatment of toluene inhalation requires that each of these clinical features be addressed. When the inhalation of toluene stops, ultimately the production of hippuric acid will be diminished, but there can be a lag of 1 – 3 days before there is little hippuric acid generation because of the large volume of distribution of toluene [21]. Hypokalemia and ECF volume contraction need to be corrected with the administration of KCl and saline, according to their severity. If metabolic acidosis is particularly severe, consideration should be given to the use of $NaHCO_3$ because there is no anion present in the body that can be metabolized to HCO_3^-. The major caveat to the use of $NaHCO_3$ in this setting is that coexisting K^+ depletion could be severe. Given the risk of a cardiac arrhythmia, the P_K must be raised first to the low 3 range before $NaHCO_3$ is administered because of the concern that $NaHCO_3$ may exacerbate hypokalemia.

Organic Acid Load from the GI Tract (D-lactic Acidosis)

Certain bacteria in the gastrointestinal (GI) tract may convert carbohydrate (cellulose and fructose) into organic acids. The three factors that make this possible are slow GI transit (blind loops, obstruction), change of the normal flora (usually with antibiotic therapy), and the supply of carbohydrate substrate to these bacteria (foods containing fructose or sorbitol [145] (Figure 24, [70]). The most prevalent organic acid is D-lactic acid [71]. Humans metabolize this D-isomer somewhat more slowly than L-lactate, but acidosis per se rarely is life-threatening. Although humans lack the enzyme D-lactate dehydrogenase, metabolism of D-lactate occurs via the enzyme D-2-hydroxy acid dehydrogenase.

There are three additional points that should be noted with respect to D-lactic acidosis. First, the usual clinical laboratory test for lactate is specific for the L-lactate isomer. Hence the usual laboratory measurement for lactate will not be elevated. Second, GI bacteria produce amines, mercaptans, and other compounds that may cause the clinical symptoms related to CNS dysfunction (personality changes, gait changes, confusion, etc.). Third, some of the D-lactate will be lost in the GI tract or in the urine (if the GFR is not too low) [146, 147]. Hence the degree of rise in the plasma anion gap may not be as high as expected for the fall in the P_{HCO3}.

Treatment should be directed at the GI problem. The oral intake of fructose and complex carbohydrates should be decreased. Antacids should be avoided to decrease the rate of fermentation. Insulin may be helpful by lowering the rate of oxidation of fatty acids and hence permit a higher rate of oxidation of organic acids (Figure 25). Antibiotics could be considered to change the bacterial flora.

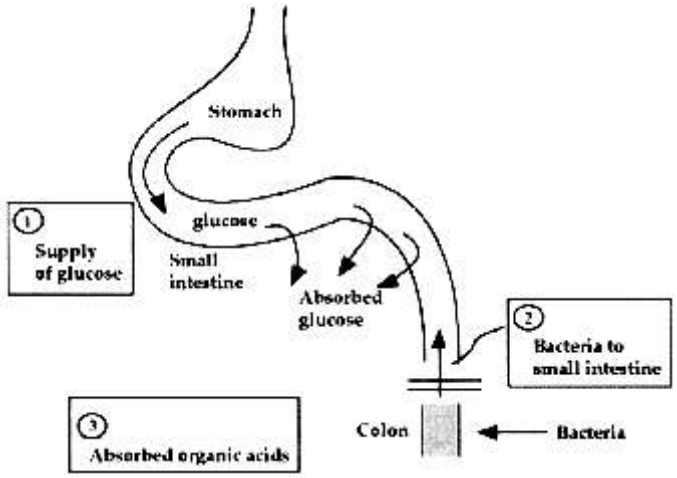

Figure 24. Organic acid production in the GI tract. Bacteria are normally segregated from dietary sugar by GI "geography". For overproduction of D-lactic acid, bacteria in the lower GI tract must mix with sugars. The supply of sugar is critical for organic acid production. Bacteria migrate up to and proliferate in the small intestine. When provided with sugar in this "friendly environment", fermentation produces a variety of organic acids and noxious alcohols, aldehydes and amines; more are produced if more alkali is supplied. There must also be enough mucosal surface area to transport these acids into the body and cause the high plasma anion gap; otherwise the H^+ produced might simply destroy luminal HCO_3^- from the secreted $NaHCO_3$ and lead to the loss of Na^+ plus D-lactate in the stool (a normal anion gap type of metabolic acidosis). The degree of the acidosis also depends on the rate that these organic acids can be oxidized and/or converted to glucose or fat (primarily in the liver).

Pyroglutamic Acidosis

The list of causes of metabolic acidosis with a high anion gap in plasma does not usually include pyroglutamic acidosis (PGA) because it was thought to represent primarily rare inborn errors of metabolism in the glutathione synthesis pathway (defects in 5-oxoprolinase or in glutathione synthetase, Figure 26) [148, 149]. Notwithstanding, there have been an increasing number of case reports where PGA accumulated and caused metabolic acidosis with an increase in the anion gap in plasma [131, 150 – 152]. When plasma levels of PGA rose to the 5 – 10 mM range, the 24-h urine contained 50 – 150 mmol of PGA [131, 150, 151]. The question raised by these observations is, what is responsible for the accumulation of PGA?

Key to the understanding of the accumulation of PGA is the fact that the reduced form of glutathione (GSH) feeds back to inhibit the enzyme (-glutamylcysteine synthetase) that catalyzes the first step in the cycle that leads to the synthesis of glutathione, the conversion of glutamate to -glutamylcysteine (Figure 26) [153].

A major function of reduced glutathione is to detoxify reactive oxygen species (ROS). In this process, the reduced form of GSH is converted to its oxidized form (GS-SG) (Equa-

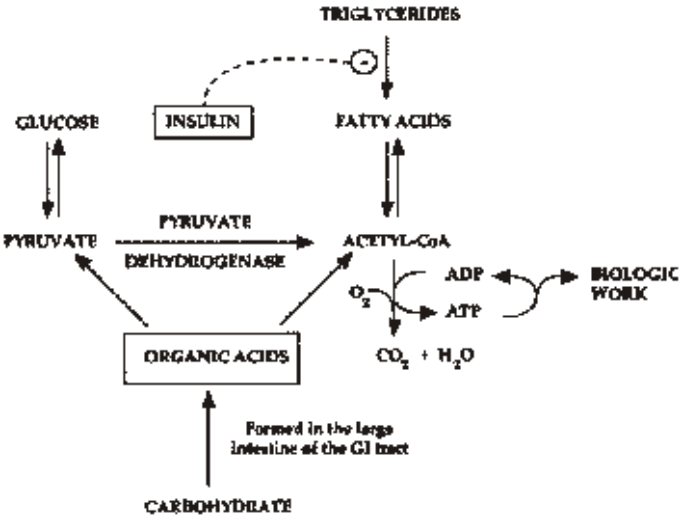

Figure 25. Strategies for therapy in D-lactic acidosis. There are two families of organic acids depending on whether they yield pyruvate or acetyl-CoA, bypassing pyruvate as a metabolic product. Organic anions that cannot be converted to pyruvate can only be oxidized, converted to storage fat, or be converted to ketoacids, but are not substrates for the synthesis of glucose. Fatty acid synthesis only occurs at appreciable rates when insulin levels are high (with meals). If insulin acts and depresses the rate of oxidation of fatty acids, more organic acids may be oxidized [70].

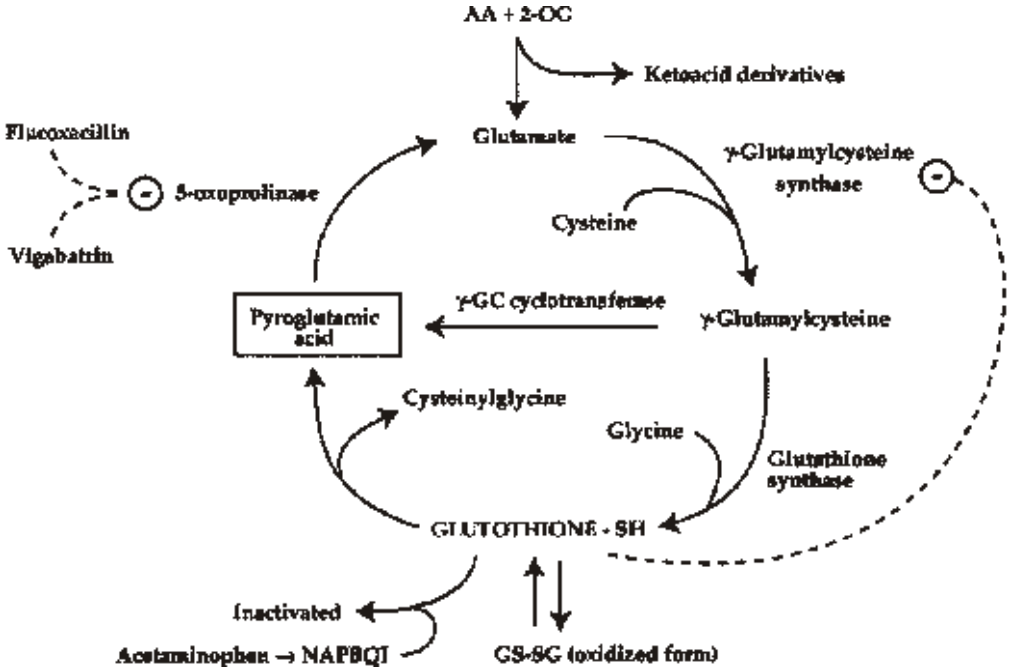

Figure 26. Production of pyroglutamic acid. The pathway begins with glutamate, a key intermediate in transamination reactions. When there are low levels of reduced glutathione (e.g., due to combination with a metabolite of acetaminophen), the production of -glutamylcysteine is stimulated. If the -glutamylcysteine so-formed accumulates, pyroglutamic acid will be formed. In addition, if 5-oxyprolinase is inhibited, pyroglutamic acid will also accumulate. As described in the text, a diminished ability to detoxify ROS is likely to be more important than the acidosis in this setting. Reproduced with permission [187].

tion 13). Hence when ROS accumulate, the concentration of GSH declines and this leads to an accelerated formation of -glutamylcysteine (-GC). This -GC will be converted to PGA by the enzyme -glutamylcysteine cyclotransferase when its concentration rises (Figure 26). Components of the glutathione cycle reside in different compartments of the cell [1]. This adds to the complexity of understanding the regulation of this feedback system.

2 GSH + ROS GS-SG + Inactive ROS (13)

PGA can be synthesized from glutamate when an internal peptide bond forms between its -carboxyl group and the free -amino group (i.e., if glutamate is free or the N-terminal amino acid is a peptide or protein) as long as the latter's -carboxyl group is in an activated state. A number of drugs have been identified as potential causes of PGA acidosis. Some like acetaminophen, after conversion to a metabolite N-acetyl-p-benzoquinonimide (NAPBQI), decrease the concentration of GSH, thereby driving the synthesis of -glutamylcysteine, and thereby PGA (Figure 26). Other drugs (e.g., the antibiotic flucloxacillin [150] and the anticonvulsant, vigabatrin [154]) may inhibit 5-oxoprolinase. A third mode of action could be with drugs or inborn errors of metabolism (e.g., G6PDH deficiency) that result in a diminished concentration of NADPH, the cofactor that reduces GS-SG to GSH [1] (Equation 13).

Acid-base aspects: Applying concept 1 to this pathway, H^+ will only accumulate when the precursor of pyroglutamic acid is glutamine providing that the NH_4^+ so-formed is metabolized to urea in the liver (Equation 14).

Glutamine Glutamate$^-$ + NH_4^+
Pyroglutamate$^-$ + NH_4^+ Urea + H^+ (14)

Renal Acidosis

As described in Table 6, renal disorders may cause metabolic acidosis with either a normal or an increased anion gap in plasma. Most causes have in common a reduced rate of NH_4^+ excretion [56]; in contrast, with a recent onset of proximal RTA, the excretion of HCO_3^- may also contribute to the degree of metabolic acidosis. Whether the plasma anion gap will be elevated or not depends primarily on the GFR. For example, if the GFR is very low, anions such as phosphate and SO_4^{2-} need to have higher concentrations in plasma to be excreted at their usual rate. This in turn leads to a rise in the plasma anion gap (Figure 6), but it does not usually exceed 22 mEq/l or about 10 mEq/l above normal. In this semiquantitative interpretation, it is important to examine the concentration of albumin in plasma because this is the most important constituent of the normal plasma anion gap and hypoalbuminemia is not an uncommon finding in this group of patients. The possible molecular basis for a low rate of excretion of NH_4^+ (Figure 5) or a high rate of excretion of HCO_3^- is shown in Figure 27.

Clinical Approach to a Patient with HCMA

Patients who have HCMA can be divided into three broad categories based on the rate of excretion of components of net acid (Table 18). Our approach to patients with HCMA starts with an assessment of the rate of excretion of NH_4^+ (Figure 28). A low rate of excretion of NH_4^+ is the key finding in patients with distal RTA; it is also expected in patients with proximal RTA and an alkalinized PCT ICF pH. In the latter group, the low rate of excretion of NH_4^+ is usually due to a diminished rate of production of NH_4^+ because of excessive distal delivery of HCO_3^- from the PCT. If an assay of urine NH_4^+ is not available, the

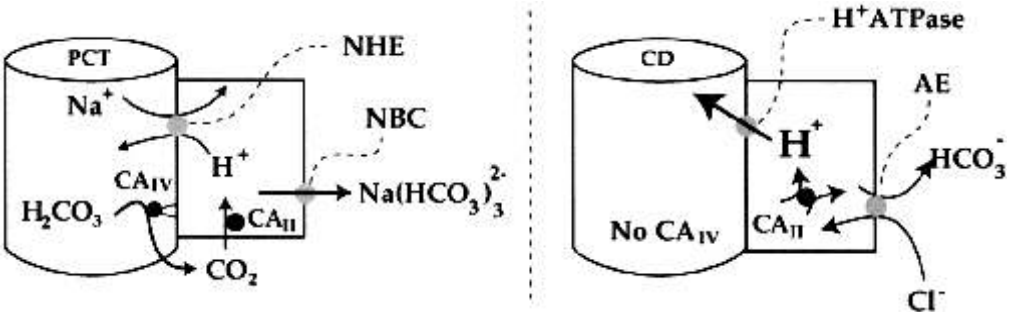

Figure 27. Molecular components for H^+ and HCO_3^- transport in the nephron. The events in the PCT are shown in the left portion of the figure and the events in the collecting duct (CD) are shown in the right portion of the figure. Carbonic anhydrase (CA) is depicted by the small solid circles. Abbreviations: NHE = Na^+/H^+ exchanger in the PCT; NBC = $Na(HCO_3)_3^{2-}$ exit step in the PCT; AE = Cl^-/HCO_3^- anion exchanger.

urine osmolal gap should be used to reflect this excretion rate (Figure 11).

If the rate of excretion of NH_4^+ is high in a patient with HCMA (e.g., overproduction of -hydroxybutyric acid) (Figure 28), a renal component to the acidosis could be present if there is a large loss of the metabolizable -hydroxybutyrate anions in the urine [155]. It should be clear that the main cause of the metabolic acidosis in this patient is overproduction of organic acids; nevertheless, the severity of the acidosis may be aggravated by the presence of a renal lesion that leads to the loss of organic anions (potential HCO_3^-) in the urine. An excessive rate of excretion of organic anions in the urine is suspected if the sum of $Na^+ + K^+ + NH_4^+$ in the urine greatly exceeds that of Cl^- (Figure 11).

In a patient with HCMA and a low rate of excretion of NH_4^+, the basis for low NH_4^+ excretion can be deduced from the urine pH. If the urine pH is greater than 7, one should examine the secretion of H^+ in the PCT (reabsorption of HCO_3^-) and in the distal nephron (Figure 28). We recommend examining the PCO_2 in alkaline urine to detect whether there

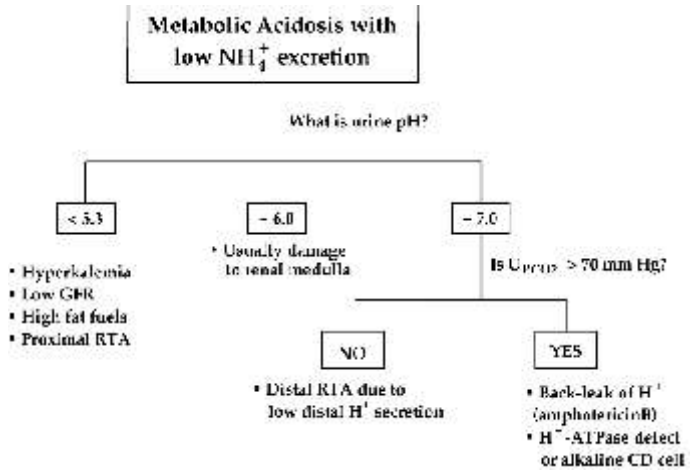

Figure 28. Approach to patients with HCMA. If there is a low rate of excretion of NH_4^+, the urine pH is helpful to determine whether a low distal and/or proximal H^+ secretion or a low NH_3 availability was the cause for the low rate of NH_4^+ excretion.

is a defect in distal H^+ secretion. If urine PCO_2 is < 70 mm Hg, a primary H^+ATPase pump defect or an alkaline -intercalated collecting duct cell pH (e.g., CA_{11} deficiency) should be suspected. This latter lesion also involves the PCT, causing proximal RTA. If urine PCO_2 > 70 mm Hg, suspect a back leak of H^+ from the collecting duct or a defect causing distal HCO_3^- secretion (e.g., a mis-targeted Cl^-/HCO_3^- anion exchange.

HCMA with a low rate of excretion of NH_4^+ and a low value for the urine pH (the actual value is difficult to define precisely, but we consider a low value to be less than 5.3) suggests that there is a reduced availability of NH_4^+/NH_3 in the renal medullary interstitial compartment (Figure 12). The usual causes for the low NH_4^+/NH_3 subgroup are a low GFR or hyperkalemia (Table 18). In their absence, we would look for low levels of glutamine [158], the substrate in plasma for renal ammoniagenesis, and/or a high level of fat-derived fuels (e.g., patients on TPN), because these fuels may compete with glutamine as the source for regeneration of ATP in cells of the PCT [159], and hence lead to a lower rate of production of NH_4^+. Patients with proximal RTA also have a low rate of excretion of NH_4^+. This could be due to an alkaline PCT cell or it could be part of a generalized PCT cell dysfunction (the Panconi syndrome [156, 157]). Both of these groups of patients will have hypercitraturia despite the presence of metabolic acidosis. In the former group, the hypercitraturia is due to an alkaline PCT cell and may disappear if an acid load were administered. In the latter group, the hypercitraturia is part of the generalized PCT cell transport defects.

Loss of $NaHCO_3$ in the Urine

The initial mechanism for the acidosis in patients with proximal RTA is the loss of HCO_3^- in the urine. In contrast, once a steady state supervenes, chronic metabolic acidosis is sustained because the rate of NH_4^+ excretion is much lower than expected in this setting [30, 31]. As mentioned above, these patients will have hypercitraturia despite having metabolic acidosis. The defect in proximal HCO_3^- reabsorption can be demonstrated by finding a FE_{HCO3} that exceeds 10 – 15% during $NaHCO_3$ loading. This, however, need not be performed because the diagnosis is usually evident when large doses of $NaHCO_3$ fail to the P_{HCO3} the normal range. Proximal RTA can occur as an isolated defect [160] or as part of a generalized proximal tubular cell dysfunction (Fanconi's syndrome with a glucosuria, phosphaturia, aminoacidosis, uricosuria and citraturia among others) [156]. The major causes of proximal RTA in adults include increased blood levels of monoclonal immunoglobulins found in patients with multiple myeloma and patients who use the carbonic anhydrase inhibitor, acetazolamide. In contrast, cystinosis [161] and the use of ifosfamide [162] are the most common causes of proximal RTA in children. The hereditary isolated proximal RTA is a rare autosomal recessive disease that can present with ocular abnormalities such as band keratopathy, cataracts and glaucoma [163]. Mutations in the gene encoding for the $Na(HCO_3)_3^{2-}$ cotransporter (NBC1) has been identified in these families. The autosomal dominant form may be caused by mutations in the gene for NHE [164].

Recently, the use of Chinese herbs was described as a cause of the Fanconi's syndrome [165]. Typical Chinese herb nephropathy is associated with acellular interstitial fibrosis and tubular atrophy. Some of these patients

have a profound degree of hypokalemia with muscle paralysis as the presenting feature [166]. Hypokalemia in other causes of the Fanconi's syndrome is usually absent or mild in degree.

The pathological mechanisms of Fanconi's syndrome due to Chinese herb remain unclear. Aristolochic acid found in the Chinese herb has an inhibitory effect on calcium-dependent phospholipase A_2. This may in turn lead to a defect in energy-producing or energy-linked transporting mechanisms and/or have a direct toxic effect on the brush-border membrane of the tubular cells that may cause renal tubule injury with the resultant Fanconi's syndrome.

From a therapeutic standpoint, the acidosis in these patients is usually mild and complications due to the acidosis are minor. These facts alone argue against alkali therapy in adults. In addition, if exogenous $NaHCO_3$ is given, as the P_{HCO3} rises temporarily, but its excretion will also rise markedly. A large increase in delivery of Na^+ and HCO_3^- to the CCD may augment the secretion of K^+ [84], resulting in hypokalemia and possibly nephrocalcinosis. In contrast, alkali therapy is useful in children to prevent growth retardation [167].

Cause of a Low Rate of Excretion of NH_4^+

Renal failure: As the GFR falls, the synthesis of NH_4^+ declines in the PCT due to ATP turnover constraints [33]. Metabolic acidosis is therefore a common finding with advanced renal insufficiency, although the degree of acidosis is variable. It is rarely severe enough to require urgent therapy with $NaHCO_3$. On the other hand, chronic metabolic acidosis may contribute to fatigue and anorexia, and also skeletal muscle wasting [168] and bone disease [169]. Therefore it is reasonable to give oral $NaHCO_3$ to these patients to maintain the P_{HCO3} close to 20 – 25 mM making certain that the Na^+ load does not lead to hypertension or congestive heart failure. With the onset of dialysis therapy, acid-base balance is maintained by the addition of $NaHCO_3$ or a metabolic precursor of HCO_3^- (e.g., acetate, L-lactate) added to the dialysis fluid.

Distal RTA (classical RTA): The hallmark of distal RTA is a low rate of excretion of NH_4^+ in a patient with chronic metabolic acidosis, a normal value for the anion gap in plasma, and a GFR that is not markedly reduced [56]. Having defined these components, the next step is to find out why the rate of excretion of NH_4^+ is lower than expected in this setting. We rely on the urine pH at this point to separate the patients into 3 categories, those with a primary problem with NH_3 availability (urine pH less than 5.3), those where there is a structural lesion in the renal medulla that compromises both medullary NH_3 availability and distal H^+ secretion (urine pH close to 6), and those with a defect in net distal H^+ secretion (urine pH close to 7). In this latter group, the low rate of excretion of NH_4^+ is due primarily to reduced distal H^+ secretion per se and/or to an excessive amount of HCO_3^- delivered to or secreted in the distal nephron (Figure 29). Generalized medullary damage with a urine pH that is close to 6 is the most common clinical subgroup [53]. Autoimmune disorders (such as Sjögren's syndrome and rheumatoid arthritis, hypergammaglobulinemia) are the most common causes of distal RTA with a very high urine pH in adults [56]. RTA in patients with Sjögren's syndrome seems to be due to a defect in H^+ secretion in the distal nephron. In some of these patients, there was an absence of the H^+-ATPase pump in intercalated cells of the collecting tubule as revealed by an immunocytochemical analysis of tissue obtained by renal biopsy [170]. It is not known how the immune injury leads to the loss of

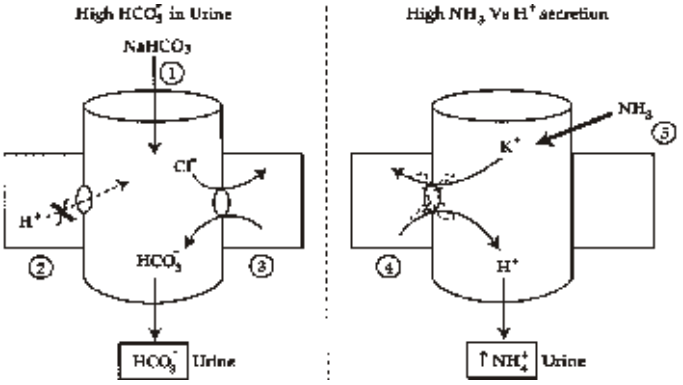

Figure 29. Basis for a high urine pH. There are two subgroups to consider. First, those where the net addition of HCO_3^- by failing to reabsorb $NaHCO_3$ in upstream nephron segments (site 1) or via secretion in the MCD via AE (site 2), exceeds the usual H^+ secretion by the H^+-ATPase in the CCD and MCD (site 2). Second, as shown to the right of the dashed line, those where there is a high medullary NH_3 concentration (due to enhanced PCT production of NH_4^+, site 5) exceeds the secretion of H^+ by the H^+/K^+ ATPase in the MCD (site 4).

H^+-ATPase activity. It has also been suggested that the defect may be due to autoantibodies against carbonic anhydrase II, as high levels of these antibodies were detected in some patients. If these antibodies could enter cells, one would also expect to find a defect in H^+ secretion in the PCT. Ifosfamide, an analog of cyclophosphamide, is also a cause of proximal and distal RTA in both children and adults [162].

Hereditary RTA is most common cause in children [171]. Familial distal RTA is inherited in both dominant and recessive patterns. The autosomal dominant form is associated with mutations in the gene encoding for the AE [172]. Red blood cells of these individuals display normal AE polypeptide abundance. These mutant forms show only a modest reduction in function and do not have a dominant negative effect when expressed in heterologous systems. It is not clear how these mutations lead to the phenotype of distal RTA. In vivo defects in stability, trafficking or sorting of these mutant anion exchangers are possible mechanisms. In Caucasians, AE1 has not been associated with the recessive form of distal RTA; however, AE1 mutations are the major cause of recessive distal RTA in Thailand, Malaysia and Papua New Guinea [173]. In those Southeast Asian patients in whom distal RTA is associated with ovalocytosis, compound heterozygotes of AE1 plus distal RTA mutations with the in-frame deletion ovalocytosis mutation were found [174]. Altered targeting of the mutant AE1 was suggested in one patient with distal RTA and Southeast Asian ovalocytosis because of a high U-B PCO_2 in alkaline urine [175].

Mutations in the gene encoding for the V_1 subunit B1 of the apical membrane vascular H^+-ATPase have been described to cause autosomal recessive distal RTA and bilateral sensorineural hearing loss [176]. Recessive distal RTA without deafness due to mutations in the a V_0 subunit of the H^+-ATPase have also been reported [177]. Mutations in the cytoplasmic carbonic anhydrase II are inherited in autosomal recessive fashion [178]. Patients with this disorder exhibit osteopetrosis, cerebral calcification and defect in H^+ secretion in both the PCT and the distal nephron.

While nephrocalcinosis may be a consequence of distal RTA, hypercalciuria and nephrocalcinosis seem to be the primary events leading to distal RTA in patients with

Dent's disease [179]. Dent's disease is characterized by low molecular weight proteinuria, hyperphosphaturia, hypercalciuria. The ClC-5 chloride channel has been identified as the mutated gene in patients with Dent's disease [180].

RTA with hypokalemia: Distal RTA is often complicated by hypokalemia [181] (the high luminal concentration of HCO_3^- stimulates net secretion of K^+ in the CCD [84], see Chapter on K^+ for more discussion). If distal RTA is present with a severe degree of hypokalemia (P_K < 2 mM), symptoms of muscle weakness or even paralysis might be present [182]. Of greater importance, there is a danger of a cardiac arrhythmia, especially if the EKG is significantly abnormal. Even if the degree of metabolic acidosis is severe, the administration of alkali alone could cause movement of K^+ into cells, worsening the degree of hypokalemia with resultant cardiac effects and/or acute respiratory acidosis. In this circumstance, there is a better strategy for therapy. KCl should be given first; larger amounts can be given safely by the oral or by a nasogastric tube than intravenously providing that the patient can absorb this K^+ load – i.e., that bowel sounds are present. Glucose-containing solutions should be avoided, since they may stimulate insulin release, which may cause an acute shift of K^+ into the cells. Although the addition of K^+-sparing diuretics such as amiloride will reduce the ongoing urine K^+ loss, their quantitative effect is very small and they may provoke hyperkalemia later on; hence we do not recommend their use in this setting. Administration or larger amounts of $NaHCO_3$ should be delayed until the P_K is above 3.0 mM. In the absence of serious hypokalemia, one then asks, how much alkali is required? The answer is not easy to deduce. One must ultimately give enough $NaHCO_3$ to bring the P_{HCO3} to the normal range. Thereafter, the dose of $NaHCO_3$ needed can be deduced. Since the daily normal acid load from the diet is usually about 70 mmol/day [7]. Since urine net acid excretion is usually reduced but not absent, considerably less $NaHCO_3$ is usually required. Supplemental K^+ is often needed as well.

Distal RTA with hyperkalemia: In some classifications, this is called type IV RTA. We do not think that this nomenclature is particularly helpful and prefer a classification that is based on pathophysiology (see reference Kamel et al. 1997 [56] for more discussion). Reduced excretion of NH_4^+ is commonly associated with hyperkalemia [32]. Hyperkalemia leads to reduced excretion of NH_4^+ primarily because it inhibits ammoniagenesis. This subtype of low excretion of NH_4^+ is recognized by finding a low urine pH (usually < 5.3) (Figure 30). A more detailed discussion of hyperkalemia can be found in the Chapter on Potassium in this book.

Therapy depends on the pathogenesis of the hyperkalemia and on the patients' ECF volume status. In patients with hypoaldosteronism due to adrenal disease, ECF volume and blood pressure are usually reduced and al-

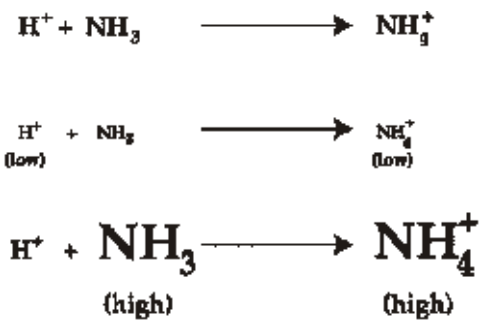

Figure 30. Types of incomplete renal tubular acidosis. The top line depicts the normal state. There are two major causes of a high urine pH. First, there is occult distal RTA due to low distal H^+ secretion in conjunction with the ingestion of a net alkali load (line 2). Second, there is an over-production of NH_4^+ in the PCT due to an acidified PCT cell, the result of a lower activity of the $Na(HCO_3)_3^{2-}$ exit step (see Figure 27).

dosterone replacement with 0.05 – 0.1 mg 9 -fludrocortisone per day plus saline administration is the treatment of choice. Glucocorticoid deficiency, if present, should be corrected. Patients with hyperkalemia due to a faster reabsorption of Cl^- in the CCD are frequently ECF volume expanded and hypertensive (see section on K^+ for more details) [183, 184]. In these patients, 9 -fludrocortisone is of no benefit for the treatment of the hyperkalemia and it may aggravate the degree of Na^+ retention. Additional therapeutic alternatives would include diuretics such as furosemide to increase the excretion of K^+ and Na^+. Correction of hyperkalemia by either mechanism should increase the excretion of NH_4^+ sufficiently to correct the metabolic acidosis.

Incomplete RTA: The cardinal features here are a high urine pH and the absence of acidemia. This persistently alkaline urine pH leads to a high urinary concentration of divalent phosphate and precipitation of Ca phosphate stones (brushite ($CaHPO_4$) stones). There are 3 possible subgroups included in this definition. In the first, a high dietary alkali load is responsible for the high urine pH. The rate of excretion of NH_4^+ is low and citrate excretion is high. The second subgroup of patients may have a high alkali intake plus reduced distal H^+ secretion. This group will have the unique finding of a low urine PCO_2 in alkaline urine. The third subgroup seem to have an acidified PCT pH despite the absence of systemic acidemia [185]. These patients have a high rate of excretion of NH_4^+ relative to their urine pH. Their intracellular acidosis in the PCT should stimulate the production of NH_4^+ and this will lead to a high concentration of NH_3 in the medullary interstitium (Figure 28). Accordingly, this higher delivery of NH_3 as compared the rate of H^+ secretion in the distal nephron will result in a urine pH that is high. Because of an acidified PCT cell pH, these patients have a very low rate of excretion of citrate, which also increases their risk of renal calcium-containing stones.

Respiratory Acid-base Disorders

Control of PCO_2 is important in acid-base physiology. Changes in the arterial PCO_2 result in alterations in the plasma H^+ concentration; far more important, however, is that a change in the venous PCO_2, which reflects the PCO_2 in cells, results in more or less binding of H^+ to intracellular proteins which could change their configuration, and thereby their function (Figure 7). The value for the arterial PCO_2 reflects the concentration of CO_2 in alveolar air required for balance between CO_2 production (metabolism) and CO_2 removal (alveolar ventilation).

CO_2 production: There is a very large production of CO_2 relative to the concentration of CO_2 in the plasma (i.e., 10 mmol of CO_2 are produced per minute, yet the arterial PCO_2 and H_2CO_3 are only 1.2 mmol of CO_2 per liter of blood). The rate of production of CO_2 is determined by the amount of metabolic and mechanical work, and to a lesser extent, the fuels being utilized (oxidation of carbohydrates yields more CO_2 relative to ATP production than does the oxidation of fat-derived fuels [2]).

CO_2 removal (alveolar ventilation): Normal ventilation is mediated by interaction between the central respiratory centers, peripheral chemoreceptors, respiratory muscles, and lung parenchyma. A major clinical task is to consider why ventilation is abnormal; this requires a detailed clinical analysis, but for brevity, it will not be provided here.

Effect of an abnormal PCO_2: With CO_2 accumulation, $H^+ + HCO_3^-$ are produced in equimolar amounts (Equation 3) even though

the P_{HCO3} normally exceeds the concentration of H^+ by close to 10^6-fold. Failure to remove CO_2 at a low enough concentration leads to respiratory acidosis because of the generation of H^+ by displacement of the BBS equilibrium to the left. Excessive ventilation causes a low PCO_2 and this results in respiratory alkalosis via displacement of the equilibrium to the right. In chronic respiratory acidosis, there is an increase in the rate of reabsorption of HCO_3^- by the PCT which results in an elevation in the P_{HCO3} which minimizes the fall in the plasma pH due to the respiratory acidosis; the converse changes occur in chronic respiratory alkalosis. Since these expected values differ in acute and chronic respiratory acid-base disturbances, it is important for the clinician to determine, on clinical grounds, whether the acid-base disturbance is acute or chronic in origin.

Although respiratory acid-base disorders are defined by changes in the arterial PCO_2, important clinical information can also be derived by interpreting the arterial PO_2. The arterial PO_2 is a function of the PO_2 of alveolar air, the diffusion of O_2 across the alveolar capillary membrane, and the degree of unsaturation of venous blood. The alveolar PO_2 is calculated as the inspired PO_2 – 1.25 X the arterial PCO_2. The A-a difference can also clarify whether hypoxemia is due to lung disease or central suppression of ventilation; in the latter case, the A-a difference should be normal. The normal value for the A-a difference depends on age and is up to 15 mmHg, but larger values are seen when more O_2 is extracted from each liter of blood in the capillary.

There are two major types of pulmonary lesions that cause the arterial PO_2 to be substantially lower than that of alveolar air:

– Blood could pass from the pulmonary artery to the pulmonary vein without perfusing alveoli that have a high PO_2 (i.e., a shunt that prevents a good exchange of air). Most lung diseases that cause hypoxemia are numerous small areas of shunting as well as areas of non-ventilated, non-perfused lung; together, these lesions lead to ventilation-perfusion mismatch.
– There might be a barrier to diffusion of O_2 from alveolar air to the capillaries in lungs. The magnitude of the A-a difference is a parameter to be evaluated when trying to decide if a pulmonary condition is improving or worsening.

While the A-a difference is widely used clinically, there are several pitfalls that must be kept in mind:

– For the calculation of the A-a difference, one utilizes the arterial PO_2 that provides a poorer reflection of the content of O_2 than does the O_2 saturation. Thus, the same reduction in O_2 content will have a different impact on the PO_2 at different sites on the oxygen-hemoglobin dissociation curve because this function is sigmoid rather than linear.
– If a fixed volume of venous blood is shunted into arterial blood, the lower its O_2 content, the greater the ultimate fall in arterial PO_2.
– If the cardiac output is lower, but the same volume of blood is shunted from the venous to the arterial side of the circulation as in normal subjects, the decline in arterial PO_2 will now be greater because more O_2 is lost on a per liter of arterial blood basis.
– The PO_2 of inspired air must be known. When patients are receiving O_2 by mask or nasal prongs, the inspired PO_2 may not be known with sufficient accuracy. Therefore, the A-a difference is most useful when patients are breathing room air or are on ventilators with a measured content of inspired PO_2.

– In the calculation of the alveolar PO_2, one must estimate the amount of O_2 removed and replaced by CO_2. To do so, one uses the arterial PCO_2 and assumes an RQ of 0.8. The RQ could be 1 if carbohydrate is the only type of fuel being metabolized and 0.7 with fat as the sole fuel.

Respiratory acidosis, clinical approach: Patients who hypoventilate can be divided into two groups: those who will not breathe appropriately (defective stimulus) and those who cannot breathe appropriately (defective respiratory "equipment"). In addition, patients with a fixed alveolar ventilation (i.e., those on ventilators) develop increased arterial PCO_2 if they have an increased rate of production of CO_2 or an increase in dead space (e.g., pulmonary embolus).

Diagnostic approach: The first step is to decide if the patient has chronic lung disease by the history, physical exam, and available past records. Next, one compares the acid-base status with that expected for that acid-base disorder (Table 4). If a discrepancy exists, a mixed disorder is present. In acute and chronic respiratory acidosis in patients who were previously normal, an empirical linear relationship has been found between the concentration of H^+ and the arterial PCO_2. In essence, there is close to a 3 – 3.5 mM change in the P_{HCO3} for every 10 mmHg parallel change in the arterial PCO_2 and close to a 1 mM change in the P_{HCO3} in acute disorders.

Patients with chronic obstructive pulmonary disease are often on diuretics and may have a coexistent metabolic alkalosis. Because H^+ stimulate ventilation, a lower concentration of H^+ can make the hypoventilation more severe. Interestingly, correction of the metabolic alkalosis in these patients does not result in a large change in their concentration of H^+; instead, there is a significant fall in both the P_{HCO3} and the arterial PCO_2, coupled with an increase in the arterial PO_2. These changes may be associated with a dramatic clinical improvement [186]. It is tempting to speculate that the clinical improvement is due, in part, to the reduction in H^+ buffering on the ICF proteins [4].

Respiratory alkalosis, clinical approach: Respiratory alkalosis is a common abnormality that is often ignored. The mortality rate associated with it in the hospital, which may well be greater than that for respiratory acidosis, reflects the importance of the underlying disease process. One can only be sure that the arterial PCO_2 is low by determining arterial blood gases in most patients. Respiratory alkalosis occurs when the ventilatory removal of CO_2 transiently exceeds its rate of production: thus, both the alveolar and arterial PCO_2 fall. At this lower level of arterial PCO_2, the daily production of CO_2 is then removed by the increased ventilation, which leads to a new steady state. A fall in tissue PCO_2 has an important impact on the concentration of H^+ in the ICF. A decrease in the concentration of H^+ results in back-titration of the protonated ICF proteins which may make these intracellular proteins less positively charged than normal, a change that could lead to altered function. Respiratory alkalosis may result from stimulation of the peripheral chemoreceptors (hypoxia or hypotension), the afferent pulmonary reflexes (intrinsic pulmonary disease), or central stimulation by a host of stimuli. In chronic respiratory alkalosis, there is a temporary small suppression of renal NH_4^+ production and excretion, and the P_{HCO3} falls (H^+ of dietary origin continue to consume HCO_3^- without equivalent renal formation of new HCO_3^-) until the plasma H^+ concentration approaches normal. Chronic respiratory alkalosis is the only acid-base disorder in which a normal plasma concentration of pH might be expected.

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Hyponatremia and Hypernatremia

Manjula Gowrishankar, Kamel S. Kamel and Mitchell L. Halperin

Introduction

This chapter is divided into 2 sections: the major concepts concerning the physiology of sodium (Na^+) and water to provide a basis for understanding dysnatremia, followed by the clinical approach to patients with hypo- or hypernatremia. This approach at times begins with therapy rather than diagnosis, if one anticipates that the dangers for the patient are imminent and/or preventable. Following a consideration of emergency issues, a plan is constructed for investigation and longer term treatment. Case examples are used to illustrate major points.

Synopsis of the Physiology of Sodium and Water

This section will explain in more detail the forces that regulate the movement of electrolyte-free water (EFW) across cell membranes; how the distribution of fluid between the 2 major compartments of the extracellular fluid (ECF), the vascular and interstitial space, is regulated; and to emphasize that the volume of the intracellular fluid (ICF) compartment is reflected by the plasma Na^+ concentration (Na^+) for the most part, because the number of particles inside most cells does not change by an appreciable amount.

Composition of Body Fluids

Water usually accounts for 50 – 70% of body mass. It is not possible to relate total body water (TBW) to body weight by a single number because the relative proportion of fat and skeletal mass, the components of body mass with little water, are not constant. Women tend to have a higher proportion of fat and therefore a lower water content per body mass (50% body weight vs. 60% for males). The elderly also tend to have a relatively lower water content because of their high proportion of skeletal to muscle mass. Infants, on the other hand, have a higher proportion of water (70%) due to their smaller proportion of adipose tissue.

TBW is contained in 2 main compartments, the ICF and the ECF. The ICF is twice as large as the ECF compartment (Figure 1). The ECF consists of plasma fluid (4% of body weight) and interstitial fluid (16% of body weight). In certain disease states, excess fluid accumulates in the interstitial space of the ECF, resulting in edema, ascites, and/or a pleural effusion.

Water crosses cell membranes rapidly through aquaporin-1 (AQP-1) water channels in the cell membranes (Table 1) until the osmolality is equal on both sides of the membrane [1]. Not all materials dissolved in water disperse equally in the ICF and ECF because of differences in permeability, the presence of transporters, and/or active pumps that regulate their distribution. The volume of each

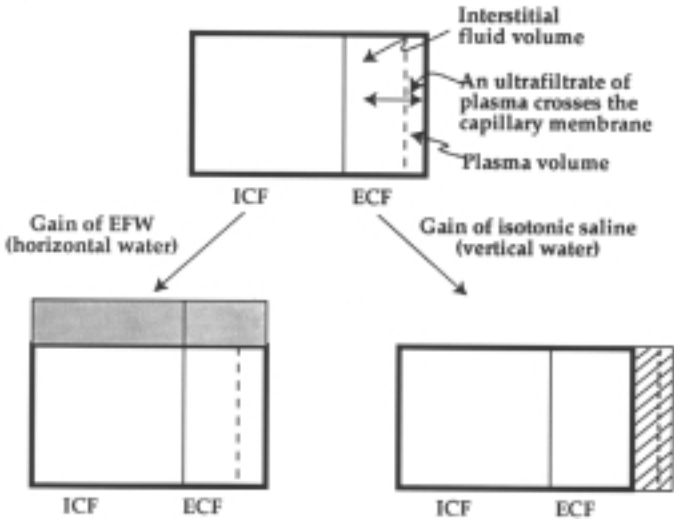

Figure 1. Body water. The rectangle in bold represents the body fluid compartments; the solid, thin, vertical line represents the membrane separating the ICF and ECF compartments; dashed, thin, vertical line separates the vascular and interstitial compartments. When there is a gain of EFW (bottom left), this water distributes in the ICF and ECF in proportion to their existing volumes (depicted by the horizontal, shaded rectangle above these normal compartments). It expands both volumes and therefore it leads to hyponatremia. In contrast, when there is a gain of isotonic saline, only the ECF volume expands (bottom right); this is depicted by the vertical, hatched rectangle. There is no change in the plasma [Na^+] or the ICF volume. Reproduced with permission [54].

compartment depends on the content of the predominant particles that are largely restricted to that compartment. Therefore, the content of Na^+ and its attendant anions in the ECF compartment determine its volume, since not only is the permeability of the cell membranes to Na^+ relatively low compared with that to K^+, but also any additional Na^+ that enters the cell is actively transported out of that cell by the enzyme Na^+-K^+-ATPase [2]. Likewise, the content of K^+ in the ICF compartment largely determines its volume. Under normal conditions, it is believed that there are roughly twice as many particles in the ICF compared to the ECF, and therefore the ICF volume is twice as large as that of the ECF (Figure 1). Some particles cross cell membranes rapidly, either via a transporter (urea) [3–5] or by diffusion (alcohol). Since their concentrations are virtually equal in the ECF and ICF of most cells they do not contribute to the "effective" osmolality or tonicity in these compartments.

The major factor responsible for water movement into cells is intracellular potassium (K^+) retention [6]. One reason for the retention is that the ICF anions are predominantly large macromolecular anions (organic phosphates) restricted to that compartment. Although these macromolecules do not exert a large osmotic pressure due to their small number, each of them bears a large number of anionic charges. Since the ICF macromolecules are largely organic phosphate esters (e.g. ATP, creatine phosphate, RNA, DNA, phospholipids) and are essential for cell function, only small net changes in their content occur in most cells. It follows that the total number of ICF particles is relatively fixed in most cells [7]. Therefore, changes in the par-

Table 1. Channels Influenced by AVP in the Nephron

I. Water channels	Most important location	Regulation by AVP
AQP-1 (also called CHIP-28)	Many cells; (e.g. proximal convoluted tubular cells)	None
AQP-2	Luminal or vesicle membranes of late distal nephron cells.	Activated, inserted, and synthesis increased.
AQP-3	Basolateral membrane of late distal nephron cells.	None
AQP-4	Basolateral membrane of late distal nephron cells.	None
II. Urea transporters (UT)		
UT	Descending thin limb of the loop of Henle and the descending vasa recta.	None
VRUT	Luminal membrane of late IMCD cells.	Yes.

AQP: aquaporin, UT: urea transporter (not vasopressin-reponsive), VRUT: vasopressin-reponsive urea transporter

ticle/water ratio in the ICF largely reflect a change in the intracellular water content. The particle/water ratio must be equal in the ECF and the ICF compartments because of the large magnitude of the osmotic pressure (100-fold greater than the mean arterial pressure). Thus, the ECF [Na^+] reflects the ICF volume in an inverse fashion in most cells, because Na^+ (and its attendant anions) accounts for virtually all of the "effective" osmolality of the ECF compartment. In contrast, brain cells can defend against large changes in their water content by varying the number of particles in their ICF compartment. This is termed regulatory volume control [8]. One mechanism used to return a swollen brain cell toward its original volume is to extrude electrolytes, which involves decreasing the content of K^+ (and usually chloride (Cl^-)) inside the cell. Another mechanism is to extrude small organic molecules such as myoinositol and other alcohols, taurine, and/or amino acids [9]. It is also possible that these osmotically-active particles are inactivated by binding rather than exrusion [10, 11]. Likewise, shrunken cells are returned toward their original volume by the influx of ions, typically Na^+. It is also possible to increase the number of small organic particles, such as amino acids or taurine [9].

Distribution of Fluid Across the Capillary Membrane

Factors controlling ultrafiltrate movement across the capillary membrane are shown in

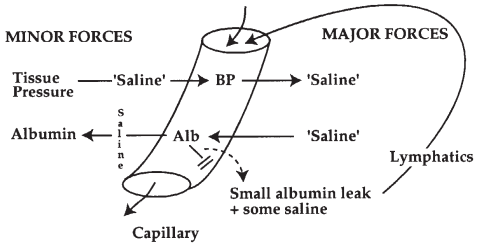

Figure 2. Events at the capillary membrane. The tubular structure is a capillary. The major outward-driving force is the capillary blood pressure and the major inward-driving force is the COP which is largely due to the effects of albumin (alb).

Figure 2. The major outward (vascular to interstitial) driving force is the hydrostatic pressure difference. When this hydrostatic pressure difference increases, as in venous hypertension (e.g. congestive heart failure (CHF)), more fluid moves from the vascular to the interstitial compartment. The major inward (interstitial to vascular) driving force is the colloid osmotic pressure (COP) difference. This is principally due to the concentration of albumin and its net anionic valence (Donnan effect). Since the intravascular compartment has a much higher concentration of albumin compared to the interstitial compartment, the COP causes fluid to move into the vascular space. When the concentration of albumin in plasma is very low, there may not be enough inward driving force and therefore the interstitial volume expands. Moreover, if capillaries become more permeable to albumin in a local area, edema fluid will accumulate. The final important component of the system is the lymphatics by which interstitial fluid is returned to the venous system.

The absolute pressure difference in mm Hg (hydrostatic pressure and COP) across a given capillary membrane is small but becomes a large force when the total capillary bed is considered. Therefore, another important factor here is the number of capillaries being perfused at any one time. If more are perfused, fluid can shift from the vascular to the interstitial compartment. If this flow exceeds lymphatic drainage, the vascular volume will be low. Since the interstitial fluid volume is so much larger than the vascular volume, any time one detects interstitial space expansion (edema), the patient will always have ECF volume expansion, even if the vascular volume may be reduced (e.g. hypoalbuminemia in patients with the nephrotic syndrome).

External Balances for Water

When a normal subject ingests EFW, it mixes with all body fluids. Two-thirds enters the ICF in steady state, while one-third remains in the ECF because water moves to osmotic equilibrium (Figure 1); thus, there is swelling of cells and hyponatremia.

Control of Water Intake

Thirst is stimulated by an increased tonicity. Particles like urea are not involved because they are not restricted to the ECF. Contraction of ECF volume is also a stimulus to thirst, but it is not a powerful one. Here, elevated levels of angiotensin II (Ang II) may act as a signal [13]. Other factors unrelated to a need for water may also stimulate water intake (e.g. dryness of the mouth, habit, social interactions). The major inhibitors of thirst are hypotonicity and, to a lesser degree, ECF volume expansion.

Control of Water Excretion

To return to steady state, the body must detect that there is a surplus of EFW (have a

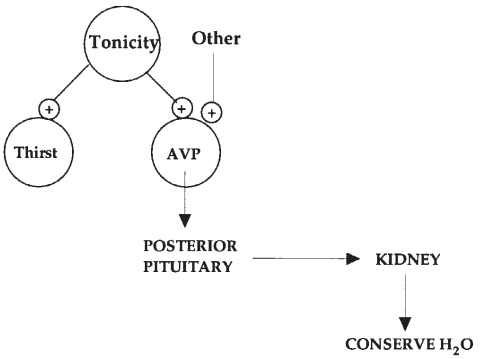

Figure 3. Control of the release of AVP and its actions on the kidney. For details, see text. The three circles represent the hypothalamic sensory system. The primary sensor is a group of cells that detect a change in their volume in response to a change in the "effective" osmolality of plasma (tonicity receptors). These cells are linked to other cells that control the intake of water (thirst center) and others that are responsible for the release of AVP. Other factors such as the "effective" circulating volume and afferent stimuli such as pain, nausea, anxiety, as well as a number of drugs also influence the release of AVP independent of the tonicity receptor influences.

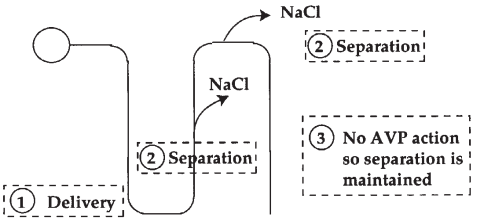

Figure 4. The excretion of dilute urine. The major structure is a stylized nephron. The numbers in the ovals represent the 3 major processes: the delivery of isotonic saline to the thick ascending limb of the loop of Henle (delivery, point 1), active resorption of NaCl from the thick ascending limb of the loop of Henle and in more distal nephron segments (separation, point 2) which generates EFW, and prevention of the reabsorption of EFW in more distal nephron segments because of a lack of AVP (maintain separation due to the absence of AQP-2 in the luminal membrane, point 3).

sensor), send a message to the kidney, and then direct the kidney to separate this EFW from its electrolytes (Na^+ salts) so that only the excess EFW can be excreted. The steps involved are as follows:

- *Sensor*: Tonicity receptors located in specialized cells in the anterior hypothalamus detect changes in cell volume [14]. This center is linked to both an area that drives thirst and another that releases arginine vasopressin (AVP) (Figure 3).
- *Messages*: Swelling of the tonicity receptor sends a message to the thirst center to diminish water intake and to the supraoptic nucleus to suppress the release of AVP. This absence of AVP translates into a message to the kidneys to excrete as much EFW as possible.
- *Renal events*: In the kidney, saline is filtered and some Na^+ and Cl^- are reabsorbed without water in the thick ascending limb of the loop of Henle and the distal nephron (Figure 4). The remaining EFW is excreted, because the luminal membrane of the distal nephron has a low permeability to water without AVP to insert aquaporin-2 (AQP-2) water channels (Table 1).

Excretion of a Dilute Urine

Excretion of EFW requires 3 steps: (1) delivery of Na^+, Cl^-, and water to distal diluting sites; (2) reabsorption of these ions without water (desalination); (3) ensuring that this EFW traverses the remainder of the distal nephron without being reabsorbed (maintenance of desalination) (Figure 4).

There are several nephron sites where Na^+ and Cl^- are reabsorbed, but water is not. The most important of these sites is the thick ascending limb of the loop of Henle. Other segments include the early distal convoluted tubule (DCT) (sparingly permeable to water

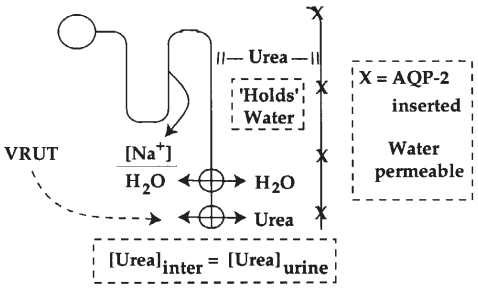

Figure 5. Formation of concentrated urine. For details, see text. There are 2 key elements operating at the renal level to excrete a concentrated urine. First, the "effective" osmolality of the medullary interstitial compartment must rise (this is represented as the Na^+/H_2O ratio in the interstitial compartment). Most important here is the active resorption of NaCl in the thick ascending limb of the loop of Henle. Second, water must be permeable across the luminal membranes of the late distal nephron (actions of AVP to insert AQP-2). The concentration of urea is elevated in the inner medullary interstitium largely because of actions of AVP to make urea permeable (VRUT is inserted) and a high concentration of urea in the urine.

even if AVP is present), the late DCT, and the collecting ducts (permeable to water in the presence of AVP).

Excretion of a Concentrated Urine

AVP action and an intact renal medulla are required to excrete a concentrated urine (Figure 5). The release of AVP from the posterior pituitary gland is stimulated by a rise in tonicity of body fluids and also by stimuli unrelated to tonicity (Figure 3) [15]. In the absence of water intake, the tonicity of body fluids rises because of ongoing EFW loss via the skin and the respiratory tract. This causes cells to shrink, particularly the tonicity receptor cells, which then causes thirst and AVP release.

AVP binds to its V_2 receptor on the basolateral membrane of cells of the late DCT and the collecting ducts, resulting in reabsorption of EFW. Three steps act to achieve this effect: the activation of AQP-2 water channels, their insertion in the luminal membrane, and the longer-term effect, the synthesis of more AQP-2 channels (Table 1) [1]. Most of the EFW is reabsorbed in the cortex when AVP acts [16]. To achieve this reabsorption, the "effective" osmolality of the interstitial fluid must exceed that of the lumen. This higher interstitial osmolality is due primarily to the active reabsorption of Na^+ and Cl^- in the thick ascending limb of the loop of Henle [16 – 18]. Thus, the passive transport of water down an osmotic difference is enhanced. As a result, a hyperosmolar urine is excreted and EFW is conserved.

Urea also contributes to the total osmolality of the interstitial fluid in the inner medulla and in the urine. In fact, it constitutes close to half the total osmolality in these locations in subjects who consume a typical Western diet. Nevertheless, if urea is permeable across the inner medullar collecting ducts (IMCD) because of the insertion of the vasopressin-regulated urea transporter (VRUT) [4, 5], it should not contribute to EFW conservation, a point illustrated in data from the rat [19]. Therefore, we prefer to think of the urine in "effective" osmolality terms rather than in total osmolality terms [20, 21].

Since one needs a hyperosmolar medullary interstitium to excrete a hyperosmolar urine, one cannot excrete a very concentrated urine in disease states where the medullary interstitium is damaged, regardless of the action of AVP.

External Balance for Na^+

People on a typical Western diet consume roughly 150 mmoles of NaCl daily. To remain in balance, 150 mmoles of NaCl must be

excreted daily. Thus, the Na^+ that was ingested must be sensed, the appropriate message sent to the kidney, and the reabsorption of filtered Na^+ in the kidney inhibited so that only the extra NaCl, and not water, will be excreted.

- *Sensor*: When NaCl is retained, the ECF volume expands. The most important component of the ECF is the "effective" circulating volume. Hence, baroreceptors in the arterial and central venous vessels detect changes in the "effective" circulating volume.
- *Messages*: The message of an increased "effective" circulating volume is delivered by renal nerves and hormones. Physical and hemodynamic factors also modulate the rate of reabsorption of Na^+ by the kidney.
- *Renal events*: In a normal adult, close to 27,000 mmoles of Na^+ are filtered each day. Of this large quantity, only a very small amount (150 mmoles, or about 0.5% of the filtered daily load) must be excreted to maintain balance for Na^+. Hence, Na^+ excretion is very tightly regulated, largely by changes in its reabsorption [22 – 24]. The first step required for the kidney to reabsorb Na^+ from the lumen is to create a driving force for the movement of Na^+ into the tubular cells. This is accomplished by lowering the $[Na^+]$ in the ICF of tubular cells, the result of the actions of the Na^+-K^+-ATPase in the basolateral membrane [2]. This transport system pumps 3 Na^+ out while transporting 2 K^+ into these cells. The Na^+-K^+-ATPase also creates an additional driving force for Na^+ reabsorption by creating a net negative voltage inside the cell. Since the luminal membrane is impermeable to Na^+, the second step required for the reabsorption of Na^+ is the insertion of specific transporters or Na^+ channels into this membrane. These transporters are specific for each nephron segment.

Na^+ Handling in the Proximal Convoluted Tubule (PCT): Of the 27,000 mmoles of Na^+ filtered each day, close to 18,000 mmoles (67%) are reabsorbed in the PCT. Co-transporters, e.g. glucose, and antiporters, e.g. H^+ on the Na^+/H^+ exchanger (NHE-3), are involved in these transport events. Electroneutrality is maintained by the reabsorption of the anions Cl^- and HCO_3^-. Since the luminal membrane here is permeable to water, the osmolality of the fluid leaving the PCT lumen is the same as that of the ECF. Ang II stimulates the reabsorption of $NaHCO_3$ in the PCT [25]. Water moves to osmotic equilibrium, thus raising the $[Cl^-]$ within the lumen. This creates a concentration difference for Cl^- which favors its passive reabsorption; Na^+ ions follow for electroneutrality.

Na^+ Handling in the Loop of Henle: Of the remaining 9 000 mmoles of Na^+ exiting the PCT lumen, 6 000 mmoles are reabsorbed in the loop of Henle. NaCl is actively transported by the Na^+-K^+-2 Cl^- co-transporter using the driving force (low $[Na^+]$ in the ICF) created by the Na^+-K^+-ATPase. The absolute reabsorption of Na^+ varies with delivery, and net reabsorption is stimulated by the action of AVP in the medullary thick limb. In the thick ascending limb, water reabsorption is negligible. Thus, the fluid exiting this nephron segment is hypotonic to plasma.

Na^+ Handling in the DCT: Close to 2 000 mmoles of the remaining 3 000 mmoles of Na^+ are reabsorbed in the DCT. Since the DCT is not permeable to water, EFW is created. Na^+ is reabsorbed with Cl^-, driven by the transepithelial $[Na^+]$ gradient across the luminal membrane of the DCT. The ion transporter

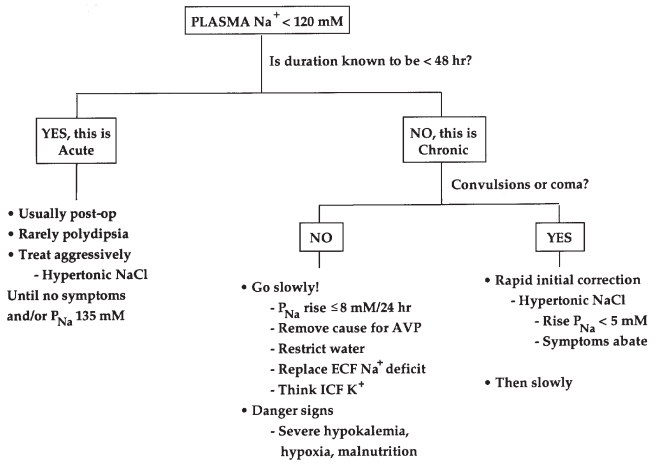

Figure 6. Approach to the patient with hyponatremia. Pseudohyponatremia and translocation type of hyponatremia should be ruled out. This figure should be examined together with Tables 3 and 4 for a more complete lists of conditions. Reproduced with permission [55].

is the Na^+-Cl^--co-transporter, which may be inhibited by thiazide diuretics. A molecular defect in this transporter causes Gitelman's syndrome (see chapter I-2, Potassium).

Na^+ Handling in the Collecting Duct: Close to 700 mmoles of the remaining 1 000 mmoles of Na^+ are reabsorbed in the cortical collecting duct (CCD) through a specific Na^+ ion channel [26]. Mineralocorticoids lead to greater opening of this channel [27], while amiloride, a K^+-sparing diuretic, inhibits it. The medullary collecting duct (MCD) reabsorbs about 150 mmoles of the remaining 300 mmoles of Na^+ delivered, so that 150 mmoles of Na^+ can be excreted to stay in Na^+ balance. In this segment, a high transepithelial [Na^+] gradient is maintained. Atrial natriuretic peptide (ANP) acts here to decrease the reabsorption of Na^+ [28], in ECF volume expansion. In contrast, during ECF volume contraction, the absence of ANP causes almost all of the Na^+ delivered to be reabsorbed.

Clinical Approach to the Patient with a Dysnatremia

General Aspects about a Patient with Hyponatremia

Is there a Major Threat to the Life of the Patient related to Hyponatremia?

The main danger in the patient in whom hyponatremia developed in < 48 hours (acute hyponatremia) is swelling of brain cells which may lead to seizures, herniation of the brain and death (Figure 6, Tables 2 and 3). In contrast, in the patient who becomes hyponatremic over a much longer time period (chronic hyponatremia), the main danger is an overly rapid rate of shrinkage of brain cell volume as a result of aggressive correction of hyponatremia. This may result in the development of an osmotic demyelination syndrome (ODS) and loss of higher cerebral functions [29]. It is important to remember that the acute discovery of a chronic condition does not make it an acute disorder.

Table 2. Overview of Hyponatremia

Type of hyponatremia	Clinical Setting	Main danger	Treatment
Acute (documented < 48 hour).	Usually postoperative.	Brain cell swelling.	Hypertonic saline to raise [Na^+] to 130 mM
Chronic	Many causes.	Osmotic demyelination.	Rise in the plasma [Na^+] should not be > 8 mM/day

Table 3. Classification of Hyponatremia

1. Acute hyponatremia (< 48 hour duration):
   a) Source of EFW:
      – Exogenous (IV or oral)
      – Endogenous = Desalination of IV or body fluids
         – Acute postoperative period
         – Cerebral salt wasting
         – Thiazide diuretics in an edematous patient
         – Giving isotonic saline to a patient with SIADH.
   b) Reason for AVP being present
      – Low "effective" ECF volume
      – Pain, anxiety, nausea, psychosis
      – Endocrine reasons (adrenal, thyroid, pituitary)
      – Metabolic disorder (e.g. porphyria)
      – Drugs
      – None of the above, see Table 5.
2. Chronic hyponatremia:
   a) Source of EFW is always needed
      – usually not the most important component of the problem.
   b) Reason for AVP (see above).

Has a Shift of Water Occurred across Cell Membranes in a Patient with Hyponatremia?

NO, the ICF volume did not change: This is the case when an isosmolar solution containing solutes other than Na^+ are added and these new solutes were retained primarily in the ECF compartment, e.g. retained lavage solution during a transurethral resection of the prostate (TURP). An example is provided in Table 4.

YES, the ICF volume has decreased in size (shrunken cells): This is the case when the solution added had both an osmolality greater than that of the ECF and the solutes that were added are retained in the ECF compartment (e.g. hyperglycemia or administration of a bolus of mannitol).

YES, the ICF volume has increased in size (swollen cells): This is the case when the solution added had an "effective" osmolality lower than that of the ECF (the addition of EFW) or hypotonic sorbitol or glycine (e.g. during a TURP) and/or the solutes added were distributed in the ECF and ICF compartments (e.g. urea or ethanol).

What is the Pathophysiology of Hyponatremia?

Two major factors should be considered and each must be analyzed independently.

There is a source of EFW: This is the more important factor in patients with acute hy-

Table 4. Comparison of EFW and isosmotic mannitol on the degree of hyponatremia. Examples are provided to illustrate the effects of retaining 3 L of EFW or 3 L of half-isotonic mannitol on the plasma [Na^+] and the volumes of the ICF and ECF. We assumed that the patient has 30 L of total body water in each case, 2/3 of body water is in the ICF compartment, mannitol will be excreted at a concentration of 300 mM during an osmotic diuresis [51, 53]. Notice the degree of change in the plasma [Na^+] when mannitol is excreted, a time with no change in the volume of the ICF compartment. This illustrates the problems relating the plasma [Na^+] and the ICF volume in translocational hyponatremia.

Parameter		Normal	Gain 3 L	Mannitol	
		Values	EFW	Gain 3 L	Excrete mannitol
Total body water	L	30	33	33	31.5
– ICF volume		20	22	21	21
– ECF volume		10	11	12	10.5
Plasma [Na^+]	mmM	140	127	114	133
– Change	mmM	0	– 13	– 26	– 7

ponatremia. In acute hyponatremia, the condition must be present for < 48 hours. As mentioned above, the major concern is brain swelling because the brain is enclosed by a rigid structure, the skull.

AVP is acting: This is the more important factor in patients with chronic hyponatremia. In the short term, one is primarily concerned with the fact that AVP might disappear and lead to too rapid a rate of correction of the hyponatremia and thereby, the development of ODS. In the long term, one is concerned with the underlying reason for AVP excess. Chronic hyponatremia includes all cases where there is a reasonable doubt about the plasma [Na^+] in the past 48 hours. If the patient is symptomatic (e.g. seizures) the worry is brain swelling and treatment is aggressive initially. If the patient is not severely symptomatic, the worry is the ODS with too rapid a rise in the plasma [Na^+].

Clinical Approach to the Patient with Acute Hyponatremia

Acute hyponatremia (developing over < 48 hours) implies insufficient time for swollen brain cells to shrink their volume back to a normal size. Due to the physical restriction imposed by the cranial vault, intracranial pressure (ICP) rises causing central nervous system symptoms, which may become serious (seizures or coma) or devastating (respiratory arrest and irreversible brain damage).

In the patient with acute hyponatremia, the emphasis at the bedside is on the source of EFW. The cause for the release of AVP is usually obvious (Table 4). The most common setting for acute, potentially life-threatening hyponatremia, is in the intra- and postoperative setting, and thus most of these cases occur in hospital. There are 3 obvious sources of EFW in this setting: (1) the administration of

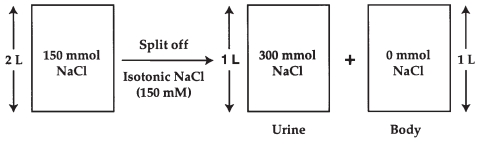

Figure 7. Desalination type of hyponatremia. The rectangles represent 1 L volumes. The [Na^+] in each L is shown in the rectangle. The left rectangle represents 2 L if IV infusions. The first rectangle to the right of the arrow represents the hypertonic urine, and the second rectangle to the right of the arrow represents the 1 L of EFW generated and retained in the body due to AVP actions. Reproduced with permission [55].

glucose in water (D_5W), or hypotonic saline as intravenous fluids (virtually always occuring in the perioperative period); (2) the intake of ice-chips or sips of water (also perioperative period); (3) the generation of EFW from the kidney excreting urine that is hypertonic to the infusate (or to body fluid in the absence of intravenous infusions [30]) (Figure 7).

Prevention: The best way to avoid acute postoperative hyponatremia is to avoid giving solutions that are hypotonic to the urine if polyuria is present, or hypotonic to body fluids in the oliguric patient. In addition, isotonic fluids should only be given to maintain systemic hemodynamics during surgery and to replace losses if they occur. One should be very suspicious of a "good" urine output because this might be hypertonic to the infused solutions and generate EFW (Figure 7). The plasma [Na^+] should be monitored in settings associated with AVP release (Table 4), particularly in patients who excrete more than 1 – 2 L of urine/day. Finally, caution should be used with the volume of fluid given to a small patient, as a large volume of fluid in a small patient translates into more EFW generation if the urine is hypertonic to the fluids administered. This is especially important in menstruous females, in whom acute hyponatremia may be more dangerous [31].

Emergency therapy: The immediate goal of therapy is to shrink the expanded ICF volume of the brain sufficiently to curtail the serious CNS symptoms. If hyponatremia is severe (< 120 mM) or symptoms are present, one should administer hypertonic saline until the plasma [Na^+] is close to 130 mM. When calculating the amount of Na^+ required, one must assume that its volume of distribution behaves as if the Na^+ will be dissolved in TBW, since the cell membrane is permeable to water, but not to Na^+ [32]. To clarify these points, consider the following illustrative case.

– *Case example:* Hyponatremia (plasma [Na^+] 120 mM) developed in a 50-kg person 24 hours after surgery; a seizure has just occurred. Therefore, the initial aim of therapy is to shrink the size of brain cells over 1 – 2 hours to the pre-seizure level. A reasonable target is to raise the plasma [Na^+] by 5 mM over the next 1 – 2 hours. In order to achieve this, 125 mmoles of Na^+ should be administered, given a TBW of 25 L (50% of body weight). Since 1 L of 3% saline contains close to 450 mmoles Na^+, 0.3 L of this solution should be administered. After the seizure is controlled, the rate of infusion may be slowed, with the goal of raising the [Na^+] to 130 mM. Careful observation is required to avoid the development of pulmonary edema.

Maintenance Therapy: Once the plasma [Na^+] has been raised to 130 mM, one should ensure that it does not fall any further. The tonicity balance approach (Figure 8) uses 2 general strategies to prevent a further fall in sodium in a patient who is excreting a large volume of hypertonic urine.

– Input: If the input is equal to the output with respect to Na^+, K^+, and water, there will be no change in the plasma [Na^+]. Since hypertonic saline is being excreted,

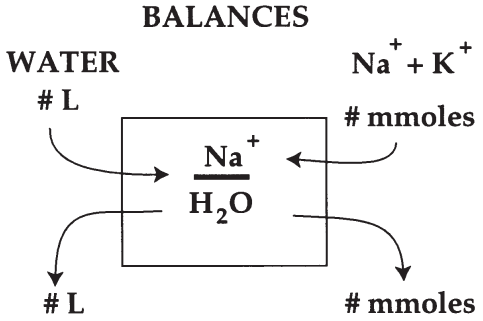

Figure 8. Tonicity balance. The rectangle represents all body compartments. To calculate a tonicity balance, one must have separate balances for water and $Na^+ + K^+$. The data can predict how the $[Na^+]$ in plasma should change; this should be compared to measured values. Reproduced with permission [55].

the same volume and the same composition of hypertonic saline must be administered.

– Output: Here the aim is to lower the concentration of Na^+ and K^+ ($[Na^+ + K^+]$) in the urine so that isotonic fluids can be administered. If the $[Na^+ + K^+]$ in the urine is very high [30], one can render it isotonic with the administration of a loop diuretic (e.g. furosemide) [33, 34] or an osmotic diuretic (e.g. urea) [35]. Isotonic intravenous fluids should be given at the same rate as that of the urine output. Once the reason for the release of AVP is no longer present, this therapy will not be required. The patient will begin to excrete dilute urine and hence the plasma $[Na^+]$ will rise [30].

Specific Examples

Acute hyponatremia in females: Most commonly, this follows otherwise uneventful gynecological surgery which leads to the sustained release of AVP for a number of reasons, such as pain, anxiety or drugs [31]. The ill-advised infusion of D_5W, the most common source of EFW in this setting, exacerbates the problem. Even isotonic saline can present the body with a large infusion of EFW [30] (Figure 7). The severity of hyponatremia may be worsened if the volume of fluid given is not scaled down to body size. This form of acute hyponatremia leads to brain cell swelling and rarely, death due to high ICP in some patients. A quantitative example is provided in Table 4.

Acute hyponatremia in males: The list of causes of acute hyponatremia in males reflects the type of surgical procedure they are likely to undergo. The most common surgery for males is TURP [36]. The main reason for hyponatremia in this setting is that large volumes of half-isotonic solutions of organic compounds are used to lavage the prostatic bed, some of which may be absorbed. The development of hyponatremia becomes clear when the absorbed fluid is divided into its two constituent parts (Table 4).

– *Gain of osmol-free (and electrolyte-free) water:* This simple EFW gain causes cells to swell, but it is not the major cause for the hyponatremia (fall of 7 mM in the plasma $[Na^+]$ in the example provided in Table 4).

– *Gain of isosmolar fluid:* Solutes such as mannitol, glycerol, or glycine distribute in the ICF compartment at a slow rate [37]. When they remain in the ECF, they cause hyponatremia because these solutions are Na^+-free. This transient form of hyponatremia is not associated with a change in brain cell volume, and so does not pose a threat of brain herniation [38]. A low plasma osmolality in the setting of acute hyponatremia following a TURP poses a threat of brain cell swelling. If that osmolality is close to normal, one should not be alarmed with the severity of the hyponatremia and the rapidity of its correction (Table 5). The symptoms

Table 5. Causes of High AVP Levels in Patients with Hyponatremia

1. AVP release in response to physiologic stimuli:
   – Low "effective" circulating volume
      – ECF volume depletion
      – Blood loss
      – Hypoalbuminemia
      – Low cardiac output.
   – Excessive pain, nausea, vomiting. or anxiety.

2. AVP release without a physiologic stimulus:
   – CNS or lung lesions.
   – Neoplasms and granulomas such as tuberculosis.
   – Metabolic lesions such as acute intermittent porphyria.
   – Administration of agents that simulate AVP
      – DDAVP (e.g. treatment for diabetes insipidus or urinary incontinence)
      – Oxytocin for labor induction.
   – Drugs that augment or stimulate AVP release:
   – Examples include nicotine, morphine, clofibrate, tricyclic antidepressants, antineoplastic agents, (probably via nausea and emesis), anticonvulsants such as tegretol.
   – Drugs that promote the actions of AVP on the kidney by increasing cyclic AMP levels or augmenting its bioactivity:
      – Examples include oral hypoglycemics (e.g. chlorpropamide), methylxanthines (e.g. caffeine, aminophylline), analgesics that inhibit prostaglandin synthesis (e.g. aspirin, non-steroidal anti-inflammatory drugs).

associated with hyponatremia when glycine is used as the lavage fluid during a TURP may be the consequence of hyperammonemia rather than swelling of cells of the brain [36].

Hyponatremia with primary polydipsia: Normally one cannot become hyponatremic simply from drinking EFW, because AVP will be absent and in this setting, normal kidneys can excrete close to 1 L of EFW/hour, more than almost anyone can drink and absorb [39 – 41]. Nevertheless, if there is a reason for AVP release, such as an appreciably low ECF volume, anxiety, pain, psychosis, or the intake of certain drugs (Table 4), the intake of EFW will result in hyponatremia [30].

Hyponatremia in an infant: Apart from unique disorders such as inborn errors, hyponatremia in this setting is most commonly due to a loss of Na^+ (e.g. diarrhea). This form of hyponatremia may be acute. AVP is released in response to the contracted ECF volume, and this leads to the retention of EFW that is ingested by the infant. If a hyponatremic infant is fed sugar water to rest the GI tract and avoid dehydration, this EFW will be retained. Thus, hyponatremia has 2 components: loss of Na^+ and gain of EFW. Its degree may be very severe. The 2 considerations for therapy include rapid re-expansion of the contracted ECF volume by infusing "isotonic to the patient" saline and avoidance of any further addition of EFW (this includes the generation of EFW by the kidneys if the rate of excretion of Na^+ were to rise while AVP is still acting, Figure 7).

Summary

– Do not give EFW to a subject with a plasma $[Na^+] < 138$ mM. Give a smaller volume if the patient is likely to have AVP released for nonosmotic reasons.
– Do not give more isotonic saline during surgery and in the acute postoperative time than is needed to maintain normal hemodynamics.
– Be careful if the urine output is larger than expected.
– Use a tonicity balance calculation to help understand the basis of hyponatremia and to plan therapy. Emphasis can be placed on changing the input or the output.

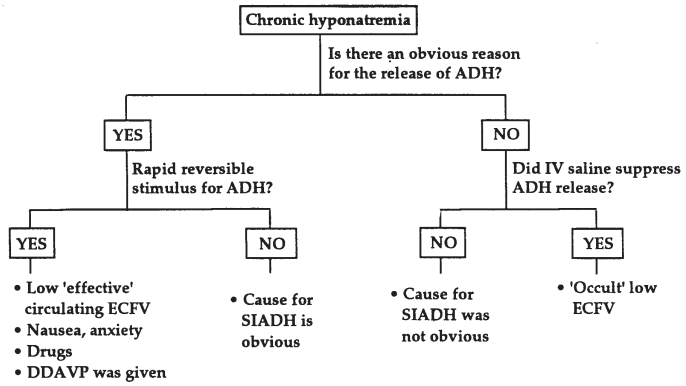

Figure 9. Steps to take in the patient with chronic hyponatremia. The focus in chronic hyponatremia is to determine why AVP is present. If the reason for the release of AVP is reversible, patients might be at risk of having a water diuresis if the release of AVP is suppressed – e.g. when their ECF volume is re-expanded. Reproduced with permission [55].

Clinical Approach to a Patient with Chronic Hyponatremia

Chronic hyponatremia is the most common electrolyte abnormality in hospitalized patients [42], but it rarely leads to significant symptoms (Figure 9). The patient with chronic hyponatremia is often identified by the determination of routine electrolytes, in which case the duration of the disorder is unknown. The fundamental issue here is that adaptive responses have had time to occur, the most important of which are in the brain. Brain cells have returned their volume virtually to normal (for review see [9]). The initial mechanism is the export of ions (K^+), providing that electroneutrality was not the result of the entry of Na^+ into their ICF (it is not clear which anion might be exported with K^+, but the defense of the ICF volume of cells of the brain would be most efficient if Cl^- were also exported from these cells). Over the next few days, organic molecules such as myoinositol, amino acids, and taurine are exported. Brain cells must reaccumulate solutes that were lost to achieve a normal ICF volume and composition; this provides the rationale for deciding the rate of correction of hyponatremia. The critical issue is that these cells, which have undergone volume regulation, are at risk of an acute decline in their volume if the plasma $[Na^+]$ is raised before these solutes are taken up. This is even more important if these cells do not have available organic osmolytes to re-establish their normal ICF osmole composition. For example, a patient with poor nutrition or a large deficit of K^+ may take longer to regain these intracellular organic osmolytes [43]. Correction of hyponatremia exceeding 6 – 8 mM/24 hours, can lead to the devastating neurologic syndrome, ODS [44].

Diagnostic Issues

To develop hyponatremia, a source of EFW (usually ingestion of water) coupled with a limitation to its excretion (release of AVP) must be present. Virtually everyone drinks EFW, so one need not dwell on this for diagnostic purposes unless the intake is very large. The diagnostic issue focuses on why the rate of excretion of EFW is so low. The challenge to the physician is to identify why AVP was released despite a low plasma "effective" osmolality (Table 5, Figure 9). The objective at the bedside is to determine whether AVP levels will decline rapidly, leading to an overly rapid rate of hyponatremia correction, thus predisposing the patient to ODS.

Several examples where the level of AVP might decline abruptly include chronic nau-

sea, vomiting, anxiety, and/or stress, or when desmopressin (DDAVP) is given to patients in a nursing home to minimize bed wetting. In addition, the apparent on-again, off-again release of AVP may be the result of a decreased "effective" circulating volume. When the "effective" circulating volume is low enough, AVP will be released, even if hyponatremia is present. This helps to defend the ECF volume at the price of an expanded ICF volume. Since thirst is also stimulated by a low "effective" circulating volume, both a source of EFW and the release of AVP to prevent its excretion are present. The problem is that a clinician may have great difficulty in deciding whether the "effective" circulating volume is contracted unless the changes are marked. One can use clues from the history. First, there may be excessive renal loss of Na^+. Its most common cause is the ingestion of a diuretic. Less often, renal salt wasting and/or an osmotic diuretic (e.g. glucose or urea) may cause excessive excretion of Na^+. In patients with renal salt wasting, examining the rate of excretion of K^+ may help determine the nephron site with defective handling of Na^+. A low rate of excretion of K^+ in the face of renal Na^+ loss and ECF volume contraction should suggest that there is a lesion in the CCD, for example a low aldosterone bioactivity. In contrast, a high rate of excretion of K^+ with renal Na^+ wasting suggests that an abnormal loss of Na^+ occurred in the PCT (usually with metabolic acidosis), the loop of Henle (as in patients with Bartter's syndrome), or the early DCT (as in patients with Gitelman's syndrome). Although one would expect a low rate of excretion of Na^+ and Cl^- when the ECF volume is low, there are notable exceptions to this rule. Na^+ may be excreted if there is a high rate of excretion of another anion such as HCO_3^- in the patient who has vomited recently. In this case, the excretion of Cl^- should be low. In contrast, if the loss of NaCl was due to diarrhea, the associated metabolic acidosis will cause a high rate of excretion of ammonium (NH_4^+) and because this NH_4^+ is excreted with Cl^-, the urine may be Cl^--rich but Na^+-poor (Table 6). Loss of Na^+ can also occur via nonrenal mechanisms. These are usually obvious (e.g through gastrointestinal tract or skin) and should be suspected when the urine is virtually Na^+-and/or Cl^--free *all* the time. The "effective" circulating volume is decreased either when the overall ECF volume is reduced or when the ECF volume is maldistributed so that there is insufficient volume in the "effective" vascular compartment, as in edema states (e.g. in patients with hypoalbuminemia). A second type of maldistribution occurs when the arterial volume is low and the venous volume is high, as when there is a primary decrease in cardiac function or venodilitation.

Table 6. Urine Electrolytes in the Differential Diagnosis of Hyponatremia. (These urine electrolyte levels do not apply to polyuric states.)

Condition	Urine Electrolyte Na^+	Urine Electrolyte Cl^-
– Vomiting		
Recent	High*	Low**
Remote	Low	Low
– Diuretics		
Recent	High	High
Remote	Low	Low
– Diarrhea or laxative abuse	Low	High
– Bartter's or Gitelman's syndrome	High	High

*High = Urine concentration > 15 mM, **Low = Urine concentration < 15 mM

Clinical Clues

Four laboratory tests might help indicate if the "effective" circulating volume is contracted.

- *Plasma [K^+]*: Either hypokalemia or hyperkalemia can suggest the reason for the release of AVP. When the ECF volume is low, release of aldosterone results in renal K^+ loss. This loss is especially high when volume and bicarbonate (HCO_3^-) delivery to the CCD are high. Therefore, hyponatremia associated with diuretics or vomiting should be suspected if hypokalemia and renal K^+ wasting are present. In contrast, patients who have hyponatremia and hypokalemia due to diarrhea may have a low rate of excretion of K^+ if their loss of K^+ occurred via the GI tract. Finally, in patients with Addison's disease (low aldosterone levels) and hyponatremia, hyperkalemia is usually present.

- *The plasma [HCO_3^-]*: The plasma [HCO_3^-] may be high in patients who have vomiting or diuretic-induced hyponatremia (metabolic alkalosis). In contrast, hyponatremia of hypoaldosteronism is generally accompanied by a mild fall in the plasma [HCO_3^-] to close to 20 mM, because of a low rate of excretion of NH_4^+ consequent to renal effects of hyperkalemia [45, 46].
- *The BUN*: In patients with the syndrome of inappropriate secretion of AVP (SIADH), the fractional excretion of urea increases, probably as a result of ECF volume expansion [47]. This together with dilution due to water retention and possibly a low protein intake results in a fall in the concentration of urea in plasma (BUN). In hyponatremia associated with a low "effective" circulating volume, there is a higher plasma urea level because the stimulus to AVP release (ECF volume contraction) leads to a fall in the GFR and an enhanced rate of reabsorption of filtered urea in the PCT.
- *The plasma urate level*: The plasma urate level may be quite low in patients with hyponatremia caused by SIADH. The mechanism is thought to be due to the expanded ECF volume in SIADH. If the ECF volume is contracted, more urate is reabsorbed and its level in plasma could rise.

Quantitative considerations: When AVP acts, the urine will contain very little EFW in patients who maintain their usual intake of salt. Nevertheless, to deduce what the anticipated changes are likely to be, one must examine the input and output, and perform a tonicity balance (Figure 8). The following examples illustrate these 2 points.

Example 1, emphasis on the source of EFW: Subjects on a normal Western diet consume 150 mmoles of NaCl and 50 mmoles of K^+, and excrete 1.5 L of urine a day. They remain in balance and their 24-hour urine [$Na^+ + K^+$] is 133 mM. Since the urine [$Na^+ + K^+$] can only rise to just over twice this value because of a limit set by medullary tonicity, positive balance for EFW can only be approximately 0.75 L/day. Said another way, it is difficult to have a large daily positive EFW balance, unless the intake of water increases appreciably and/or the intake of NaCl declines to a major extent.

Example 2, emphasis on the content of Na^+ in the ECF: An elderly woman consumes tea and toast. Her intake of EFW is not low because she drinks a large cup of tea by habit; however, her diet contains little $Na^+ + K^+$. To stay in balance, she must excrete urine with a very low [$Na^+ + K^+$]. If AVP is acting, the [$Na^+ + K^+$] in her urine can rise to close to 300 mM

[18]. Hyponatremia can develop quickly and now EFW will be generated rather than excreted (Figure 7). Hence, both the electrolyte and EFW intake, plus the capacity to have a high [$Na^+ + K^+$] in the urine, impact on the likelihood of developing hyponatremia and contribute significantly to its severity.

Clinical Settings for Chronic Hyponatremia

One first tries to identify patients with an "effective" circulating volume that is obviously contracted and those with SIADH, either from medications or a condition that may cause the release of AVP (Table 5).

SIADH: A persistently elevated level of AVP acts to limit the excretion of EFW. When EFW is ingested, much will be retained and cause hyponatremia. Initially, the ECF volume is expanded so Na^+ is excreted in the urine. Hence, the characteristic findings in steady state are hyponatremia, the absence of ECF volume contraction, and a urine which contains as much Na^+ and Cl^- as the patient is ingesting. A note of caution is needed here. Patients with SIADH who consume a low salt diet will have little Na^+ and Cl^- in their urine, so a high urine [Na^+] is not a requirement for this diagnosis. The urine osmolality exceeds the minimum value of 30 – 80 mosm/kg H_2O, which is the expected value if AVP is absent. Before establishing the diagnosis of SIADH in a patient with chronic hyponatremia, be sure that there is no reduction of the "effective" circulating volume. This might require an infusion of isotonic saline. When this is done, SIADH is ruled out if the urine osmolality declines to minimum values.

There are 4 subgroups of SIADH as shown by Robertson et al. [48]. The first subgroup is the patient with random high autonomous release of AVP. A common example is the patient with carcinoma of the lung. These patients represent 35 – 50% of those with SIADH.

The second subgroup is the patient with reset osmostat. These patients have normal regulation of the release of AVP, but it is controlled around a hypotonic setting. About 33% of patients with SIADH fall into this subcategory.

The third subgroup is the patient with failure to suppress AVP totally with hypotonicity. About 15% of patients will have SIADH in which the release of AVP is normal at a high tonicity of plasma, but not absent at low plasma tonicity.

The fourth subgroup consists of about 15% of patients with SIADH. They have no problems with the regulation of the secretion of AVP, but their kidneys are either overly sensitive to AVP, or there is a circulating AVP-like material present. Perhaps some of these patient have a very low delivery of Na^+ to the distal nephron. Because the IMCD has intrinsic permeability to water even in the absence of AVP [1], they can reabsorb water from the IMCD if their interstitial fluid compartment has a high "effective" osmolality. We have called this trickle-down hyponatremia [49].

Therapy for the Patient with SIADH

Treatment of the underlying illness is crucial, but beyond the scope of this discussion. We shall restrict our comments to the treatment rapidity of correction of hyponatremia.

– *Prevention*: Certain clinical situations are associated with chronic but reversible release of AVP (Table 5). These patients will be at risk for a more severe degree of

hyponatremia if they receive EFW, and are in danger of spontaneous excessive rapid rate of correction of their hyponatremia.

– *Active treatmen*t: Only in rare circumstances should the rate of correction of chronic hyponatremia be rapid, and then, only for a short period of time. Nevertheless, we start with rapid correction because it may be necessary in a medical emergency.

Rapid correction: Use aggressive treatment only for those patients whose symptoms are very serious (e.g. seizures or coma). In this setting, one wishes to shrink the size of brain cells to that present before onset of symptoms. In practice, this means that hypertonic saline should be given to raise the plasma [Na^+] to a level where the seizure activity is not present (usually a rise in serumNa of up to 5 mM). The amount of Na^+ without water to give is 5 mmoles/L of TBW. Nevertheless, do not let the rise in plasma [Na^+] exceed an overall 24-hour rate of 8 mM [44].

Caution: With an acute seizure, the plasma [Na^+] may rise by 10-15 mM because of an acute shift of water into muscle cells, so the plasma [Na^+] at the time of the seizure may be artificially elevated. Therefore, the plasma [Na^+] should not be raised by 8 mM above the first recorded plasma [Na^+] drawn immediately after a seizure.

Slow correction: The objective here is to choose a rate of correction with which virtually no patient is known to have developed ODS (< 8 mM/day) [44]. The rate of correction should be made even slower if the patient could have difficulty with the availability of K^+ and/or organic osmolytes (e.g. alcoholics, patients with hypoxia, malnutrition, or those with a catabolic state such as burn victim) [43].

Specific Emphasis for Therapy

We can identify 3 components which should be addressed in the patient with hyponatremia, each of which requires specific therapy. These will be discussed in the following paragraphs and then be applied to the management of 3 hypothetical patients.

– *Return the ICF volume to normal*: Cells have an excess of EFW which they must lose at a slow rate. This requires a negative balance for EFW. Hence, EFW input should be limited, and strategies should be employed to increase its loss.

– *Return the composition of the ECF to normal*: Most patients with SIADH have a near-normal ECF volume. Nevertheless, the ECF [Na^+] is lower than normal. Therefore, to maintain a normal ECF volume, when EFW is lost, there must be a positive balance for Na^+. By examining quantitative changes (Figure 8), one can appreciate the importance of the Na^+ deficit.

– *Return the composition of ICF to normal*: The issues regarding a surplus of EFW in the ICF compartment have been considered above; 2 remaining aspects are restorating the K^+ deficit, if needed, and restorating the organic osmolytes of the ICF of the brain. If a K^+ deficit was present, it should be replaced with KCl. In the ICF, KCl creates a positive balance for K^+ and a negative balance for Na^+ and H^+. In the ECF, there is a positive balance for Na^+ and Cl^-. Since the KCl is usually given in a hypertonic form, there will be a net gain of hypertonic NaCl in the ECF, a rise in natremia and an expanded ECF volume. If the ECF volume was normal to begin with, the final step is to facilitate the excretion of the extra ECF volume as "isotonic to the patient" NaCl. The time course needed to restore intracellular or-

ganic compounds lost in the development of hyponatremia is a very important consideration. An even slower rate of correction of hyponatremia is prudent when there is a hypokalemia in a patient who is malnourished or has an intensely catabolic state (e.g. burn victim), and/or hypoxia [43].

Case Examples

The following 3 cases are provided to emphasize that the first step in therapy might differ in individual patients with chronic hyponatremia.

- *Case 1, focus on the ICF volume:* You are asked to treat the hyponatremia in a 50-kg person with SIADH due to a tumor. Plasma [Na^+] is always approximately 126 mM and plasma [K^+] is 4.0 mM. No symptoms are attributable to hyponatremia. The ECF volume is normal and the patient consumes a usual diet (150 mmoles NaCl per day).
- *Discussion of Case 1:* There is no urgency here. This patient will need to lose close to 2 L of EFW (the plasma [Na^+] is decreased by 10% so, without a change in the number of particles in the ICF, the ICF volume would be expanded by 10% or 2 L, if the ICF volume in this patient is close to 20 L). The course for this therapy will be several days. The simplest approach is to reduce the intake of EFW to close to less than its rate of excretion. The deficit of NaCl in the ECF can be restored without supplement because the diet has an abundant amount of NaCl. If this therapy does not work, the next step would be to increase the excretion of EFW in the urine. The best way to increase the excretion of EFW is to add osmoles such as urea to force the excretion of water at a given high urine osmolality [35]. In general, the addition of 400 mmoles of urea (24 g) will cause the excretion of 1 L of EFW. Another strategy is to use a loop diuretic to cause the excretion of isotonic saline. In this case, replacing all the ions excreted without water will cause a loss of EFW [33, 34].
- *Case 2, focus on the ECF volume:* A 50-kg person who consumes a low salt diet had a thiazide diuretic prescribed for hypertension. Current symptoms are weakness, a lack of energy, and a feeling of light-headedness upon standing. The "effective" circulating volume is contracted on physical examination (blood pressure is now 135/70 mm Hg (previously160/90 mm Hg) and there is a 20 mm Hg postural drop in blood pressure). Hyponatremia (115 mM) and a low plasma [K^+] (3.4 mM) are present. Urine output is close to 1 L per day with diuretic use. What should the therapy be?
- *Discussion of Case 2:* For now, it is safe to ignore the ICF volume and its composition. The aim of therapy is to administer 1 to 2 L of "isotonic to the patient" saline to reexpand the ECF volume. However, there is a major potential risk in this patient. If the release of AVP was due to a low "effective" circulating volume, when this volume is re-expanded, secretion of AVP may cease and a large water diuresis could occur. If therapy is not changed, the plasma [Na^+] would now rise too rapidly, making ODS more likely. Therefore, AVP should be available at the bedside and be used if the patient excretes enough dilute urine to raise the plasma [Na^+] by more than 8 mM/day.
  One other point merits emphasis. Since the patient is consuming a low salt diet and has a large deficit of Na^+ in the ECF (a deficit of 2 L of ECF volume and a

deficit of 39 mmoles of Na^+ in each of the remaining 8 L of ECF (200 mmoles) because the plasma [Na^+] is 115 mM rather than the normal value of 140 mM), a positive balance of 400 to 500 mmoles of NaCl is needed. Once the ECF volume is near normal, the design of therapy reverts to contracting the ICF volume as described for Case 1 above.

– *Case 3, hyponatremia with a severe degree of hypokalemia:* A 50-kg person was placed on a low-salt diet and a thiazide diuretic for hypertension. The clinical condition of the patient has deteriorated over the past month. Several new findings are present: a poor attention span, a general lack of interest in events, profound weakness, and depression. There are no seizures or coma. On physical examination, the ECF volume appears normal (but it could be low). On laboratory examination, there is both a profound degree of hyponatremia (103 mM) and hypokalemia (1.8 mM). The EKG reveals changes consistent with hypokalemia, but there are no cardiac arrhythmias. What should the therapy be?

– *Discussion of Case 3:* The presence of this severe degree of hypokalemia has 3 major implications: a danger of a cardiac arrhythmia, a need to treat with K^+ rather than Na^+ salts, and a much greater risk of developing ODS [43]. Therefore, there are several issues here for acute therapy. One must first lessen the degree of hypokalemia to decrease the risk of developing a cardiac arrhythmia by giving oral KCl if bowel sounds are present (see Chapter I-2 on Potassium for details). Raising the plasma [K^+] to 3 mM is a reasonable initial target, but one cannot tell in advance how much K^+ will be required. If the load of KCl expands the ECF volume too much, a loop diuretic can be administered to return this volume to normal. DDAVP should be given if a large water diuresis occurs because of suppression of the release of AVP. The overall rate of correction of hyponatremia should not exceed 8 mM/day. There is also a greater danger of developing ODS in patients with hyponatremia and hypokalemia, so the rate of correction of hyponatremia should be even slower than usual (~ 5 – 6 mM/day). As in Case 2, one will need to add NaCl to the diet to repair a deficit of NaCl in the ECF.

Summary

– Do not let the plasma [Na^+] rise by more than 8 mM/day in a patient with chronic hyponatremia.
– Watch out for a water diuresis if AVP is likely to disappear.
– Do not give KCl quickly once the plasma [K^+] rises above 3.0 mM.

General Aspects about a Patient with Hypernatremia

Definition: Hypernatremia is a plasma [Na^+] > 144 mM. It is always associated with a low ICF volume; but the ECF volume may be normal, increased, or decreased.

Illustrative case: A 33–year–old woman has been on lithium for a bipolar affective disorder. While on the medication, her urine volume has increased appreciably, and she feels thirsty when she wakes up at night. She had a surgical procedure under general anesthesia early today. There were no complications in the operating room. Her perioperative intravenous fluid infusion was 3 L of isotonic saline. In the recovery room, she excreted 3 L

of urine, and her plasma [Na^+] rose to 149 mM. The urine osmolality was 107 mOsm/kg H_2O and the urine [Na^+] was 35 mM. What is the basis for her hypernatremia and how should she be treated?

Clinical Approach to the Patient with Hypernatremia

Hypernatremia indicates a negative balance for water and/or a positive balance for Na^+, although often both are responsible (Table 7). Four factors need to be assessed to determine the basis for the hypernatremia [50]. First, there will always be a disturbance of the thirst mechanism. Second, often there will be an inappropriate renal response. Third, in some cases, there will be a problem with excessive administration of Na^+, so one should evaluate the ECF volume. Fourth, one should ask about a loss of weight, since a negative balance of 1 L of EFW should cause a 1 kg weight loss.

– *Analysis of thirst:* The main defense against a reduced cell volume, as seen in hypernatremia, is to increase water intake by stimulating thirst. Because thirst is so effective, it is virtually impossible to increase the plasma [Na^+] by more than a few mM if water is available and the drinking mechanism is intact. Therefore, patients will only develop hypernatremia if they cannot appreciate thirst (e.g. patients who are unconscious or under anesthesia, as in this case example), are unable to communicate their desire for water, or if they have a decreased access to water (e.g. infants or elderly suffering from a stroke). Less frequently, hypernatremia occurs in patients with a primary defect in the thirst mechanism. Rarely, the basis for the negative water balance is reduced intake of water due to vomiting or mechanical obstruction of the upper GI tract (e.g. an esophageal tumor).

  In the above case, general anesthesia and a restricted access to water contributed to the development of hypernatremia.

– *Assessing the renal response:* The expected response to hypernatremia is the release of AVP. Therefore, urine volume should be as low as possible and the urine osmolality should be as high as possible. On a typical Western diet, one might expect a urine flow rate of approximately 0.5 ml/min and a urine osmolality > 900 mosm/kg H_2O. Failure to achieve these values indicates that an abnormal respon-

Table 7. Causes of Hypernatremia. Remember that hypernatremia is always accompanied by a reduced water intake.

A. Net primary water loss
– Reduced water intake
– Defective thirst due to altered mental state, psychological disorder, disease involving the osmoreceptor or cortical thirst center
– Inability to drink water
– Lack of water
– Increased water loss
– Renal loss: central DI, nephrogenic DI usually due to lithium or an osmotic diuresis
– Gastrointestinal loss: vomiting, osmotic diarrhea
– Cutaneous loss: sweating, fever
– Respiratory loss: hyperventilation, fever
– Water shift into the ICF
– Convulsion, rhabdomyolysis
B. Net primary Na^+ gain
– Infusion of NaCl with a higher concentration than that in the urine during polyuria
– Hypertonic NaCl or $NaHCO_3$ infusion
– Ingestion of sea water or NaCl replacing sugar in the feeding formula

DI: diabetes insipidus

se is present in most circumstances. The caveat is that one is comparing results in a patient whose osmolar excretion rate may not be the usual 600 – 900 mOsm/day.

A large loss of EFW usually occurs through the kidney (e.g. in diabetes insipidus (DI) or osmotic diuresis). Other sites of a large loss of EFW are the gastrointestinal tract (e.g. gastric suction or osmotic diarrhea) or the skin, because sweat is a hypotonic solution. Loss of water via the lungs can occur with hyperventilation, but the magnitude is not usually large.

In the above case, the low urine osmolality indicates that DI is present. The patient was given DDAVP, but there was no decrease in the urine flow rate or increase in its osmolality. Therefore, the diagnosis is nephrogenic DI, most likely due to lithium.

– *Excessive administration of Na^+:* Excessive intake of Na^+ in a normal subject does not lead to hypernatremia because the thirst mechanism is intact. Nevertheless, the basis for hypernatremia is revealed by calculating a tonicity balance (Figure 8). Excessive infusion of Na^+ can cause hypernatremia when there is an infusion of a large volume of fluid with a $[Na^+]$ higher than the urine $[Na^+]$ in a patient with polyuria due to diabetes mellitus (urine $[Na^+]$ approximately 50 mM [51]) or DI (even lower urine $[Na^+]$). Other examples include giving a large infusion of hypertonic NaCl inadvertently, the accidental entry of Na^+ into maternal circulation during abortion induced with hypertonic saline, or the administration of a large amount of hypertonic $NaHCO_3$ during cardiopulmonary resuscitation for the treatment of lactic acidosis.

In subjects who have contraction of their ECF volume and a dietary or intravenous source of Na^+, renal retention of Na^+ will contribute to hypernatremia. In fact, in patients with chronic hypernatremia due to water loss (e.g. DI), Na^+ retention may play a more important role than water loss to achieve hypernatremia.

In the above case, the tonicity balance reveals that there is an even balance for water (3 L in and 3 L out), but there is a positive balance for Na^+ of close to 300 mmoles (Figure 8). If her normal total body water is 30 L and the plasma $[Na^+]$ is normally 140 mM, then her plasma $[Na^+]$ should rise to 150 mM, close to the observed value of 149 mM. There should be a shift of 1.5 L of water from her ICF to her ECF in this case (new ECF volume = (149/140) × 10 L)). Clinically, however, this degree of ECF volume expansion may be difficult to detect on physical examination.

– *Loss of weight:* Since water is the most abundant constituent of the body, a loss of water leads to a loss of weight. Quantitatively, 1 L of water weighs 1 kg. However, weight changes are notoriously inaccurate unless the changes are large. If weight was measured in our case, there would be no loss of weight, suggesting that a gain of Na^+ was the basis for her hypernatremia. Similarly, there would be no change in weight in a patient where a shift of water into cells was the basis for the hypernatremia.

Treatment of the case patient: Hypernatremia can be treated either by the addition of water or the removal of Na^+. The choice depends on the Na^+ and water content in the patient. If depletion of water is the cause of hypernatremia, water needs to be added. If Na^+ excess is the cause, Na^+ needs to be

removed (Figure 8); this is the basis for hypernatremia in the case. We would recommend giving a loop diuretic to induce the excretion of isotonic saline and replace this volume with half-isotonic saline. Since this causes a net loss of 75 mmoles of Na^+ per L of urine, we anticipate that 4 L of exchange will be needed. Water should be given by the oral route as soon as possible.

Treatment of the Patient with Hypernatremia

– *Short-term treatment:* The principles here are to defend the ECF volume rapidly, if needed, while attending to the ICF volume more slowly. When the most important problem is a severe deficit of water, isotonic (0.9%) NaCl or 0.45% NaCl should be given initially to stabilize the "effective" circulating volume. In acute symptomatic hypernatremia, the plasma [Na^+] may be reduced by 2 mM/hour for the first 3 – 4 hours, but thereafter, the rate of decline should not exceed 1 mM/hour. As with hyponatremia, chronic hypernatremia usually does not cause central nervous system symptoms, and therefore does not require rapid correction. A safe rate of correction is a 10% fall in serum sodium over 24 hours. Avoid an excessive fall in the plasma [Na^+] because a rapid reduction of the plasma osmolality may result in brain cell swelling. The amount of water needed to correct hypernatremia can be estimated with the following equation: *Water deficit (in L) = TBW X (Target [Na^+] / Current [Na^+]).*
When the EFW deficit is mild, the oral route is the safest one. If aspiration is a concern, hypotonic fluids should be given intravenously. Give intravenous solutions that are hypotonic to the urine if polyuria is present, or hypotonic to the patient in the absence of polyuria (Figure 8). Do not give glucose if the patient is hyperglycemic. In an acutely ill patient, do not give more than 300 ml D_5W/hour, because a 70-kg patient is unlikely to metabolize glucose faster than 0.2 g/hour/kg body weight [50, 52].

– *Long-term treatment:* Disorders that require chronic preventive therapy include DI and primary hypodipsia. Although DI is often listed as a cause of hypernatremia, it should be very mild in the absence of thirst defect. Treatment is therefore directed toward the curtailment of polyuria and polydipsia which disrupt lifestyle. If hormonal deficiency is the cause of DI (central DI), DDAVP should be given either in the form of nasal spray or insufflation. In the case of nephrogenic DI, treatment should be directed towards reducing the flow to the collecting duct. This can be achieved by reducing the "effective" vascular volume with a thiazide diuretic in conjunction with decreasing the intake of salt. Loop diuretics interfere with urine concentrating mechanisms by preventing the development of a high osmolality in the medullary interstitium, through prevention of water resorption in the thin descending loop of Henle secondary to decreased Na^+ resorption in the thick ascending limb. Thus, they are not as effective as thiazide diuretics in reducing collecting duct flow.

Subjects with primary hypodipsia should be taught to drink on schedule. In some instances, the thirst center can be stimulated with chlorpropamide. When the cause of hypodipsia is a disease involving the cortical thirst center or a psychological disorder, a slight increase in water intake will restore

water balance, and hence prevent hypernatremia. When hypodipsia is caused by destruction of the osmoreceptor, increased water intake will be followed by a marked increase in urine output long before the correction of hypernatremia. As the effective circulating volume is expanded by an increase in water intake, the ECF volume depletion-mediated stimulation of AVP wanes. This in turn leads to unmasking of DI, accompanied by polyuria and polydipsia. These patients will therefore have to be treated with DDAVP, as well as the intake of a set amount of water.

Measurement of body weight at regular intervals can detect net water loss leading to hypernatremia. A clinically significant increase in the plasma [Na^+] will be accompanied by a substantial weight loss. For example, if a person with a total body water of 40 L were to increase his plasma [Na^+] from 140 mM to 155 mM by pure water loss, the amount of water loss would have to be close to 4 L, or a weight loss of 4 kg.

Weight changes can also be used to guide the curtailment of water intake in those treated with exogenous AVP. If AVP action is continuously maintained by exogenous AVP administration, these patients have a form of SIADH. Unregulated intake of water can lead to hyponatremia. Daily monitoring of weight will allow one to suspect excessive water retention without measuring the plasma [Na^+]. A substantial weight gain will be accompanied by a significant reduction in the plasma [Na^+]. Another approach one can take to prevent the development of hyponatremia in patients treated with exogenous AVP is to allow the patients to develop a diuresis every few days until the patient experiences thirst. Thirst is experienced when the plasma [Na^+] rises slightly above its usual normal level. This approach of course would not be feasible in those with a disease process involving the thirst center.

Summary

- *Danger:* Hypernatremia means ICF volume contraction; the main danger is an intracerebral hemorrhage due to a reduction in ICP.
- *Diagnosis:* Four questions dominate the clinical picture:
  1. Why is there a problem with thirst?
  2. Is the renal response appropriate?
  3. Is the ECF volume contracted?
  4.Was there a loss of weight (quantitatively reflecting the negative balance for EFW)?
- *Therapy:* Reexpand the ICF volume slowly (fall in serum sodium of close to 10% per day unless hypernatremia is very acute). Maintain a normal ECF volume.
- *Caution:* There is a danger of a glucose load in a patient who needs a large, intravenous input of EFW (as D_5W). In general, do not give more than 300 ml D_5W/hr and do not give D_5W if hyperglycemia is present.

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Divalent Ion Regulation and Disorders

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Calcium

Calcium Homeostasis

Calcium, the most abundant cation in the body, represents about 2% of the total body weight. More than 99% is in bone, and is unavailable for participation in the immediate regulation of calcium homeostasis, while the remainder is distributed in the teeth, soft tissues, and the extracellular space. A 70-kg man has approximately 1.2 kg of calcium, of which only 1.3 g is extracellular. In the normal human adult, neutral calcium balance is maintained over a wide range of intakes, 500 – 1500 mg/day. In plasma, normal calcium concentrations vary from 8.8 – 10.4 mg/dL and is composed of 3 fractions. Approximately 40% of the total serum calcium is protein bound (non-ultrafiltrable). Seventy-five to 90% of this fraction is bound to albumin, and the remainder to globulin. An additional fraction (10 %) of total serum calcium is complexed to various anions, including phosphate, bicarbonate, and citrate, but is ultrafiltrable. The remainder is free ionized calcium (50%). The ionized calcium is the physiologically important component, available for transport and cellular metabolism, and can easily be measured directly. In the absence of measurements of ionized calcium, one can attempt to correct the total calcium for changes in serum protein concentration and changes in blood pH. Thus, an approximation may be obtained as follows: for every gram/dL that serum albumin differs from 4 g/dL, the serum calcium should be adjusted by 0.8 mg/dL. Similarly, for every 0.1 increment in pH, serum calcium should be decreased by 0.12 mg/dL. Generally, as blood pH decreases, the ultrafiltrable and ionized fractions increase. This increase is due not only to a decrease in the affinity of albumin for calcium but also to a decrease in calcium complexed with plasma anions, especially phosphate and bicarbonate. However, when total plasma calcium is normal, the change in the ultrafiltrable and ionized fractions with blood pH is generally insignificant except in severe acidosis (pH < 7.30) or severe alkalosis (pH > 7.60) [1]. Total cell calcium concentration ranges from 1 to 5 mM; however, most of this is bound to the external cell membrane surface, resulting in an intracellular calcium of about 0.5 mM. Most of this is either sequestered in the endoplasmic reticulum and mitochondria or bound to cytoplasmic proteins and ionic ligands, resulting in an intracellular calcium concentration of about 100 nM [1]. The precise regulation of intracellular calcium is important for its role in regulating many biological processes.

Calcium Metabolism

Normal plasma calcium concentration is maintained by the close regulation of intesti-

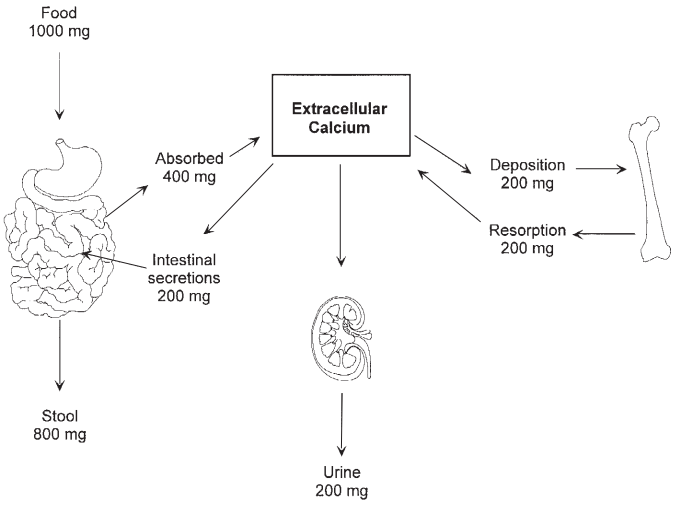

Figure 1. Scheme for calcium balance.

nal calcium absorption, renal calcium reabsorption, and retention and release of skeletal calcium. These 3 biological processes are regulated by the combined effects of parathyroid hormone (PTH) and vitamin D. The overall scheme for calcium balance is depicted in Figure 1. On a usual daily intake of approximately 1000 mg, a net absorption of 200 mg will occur. About 200 mg will enter and leave the bone, and approximately 200 mg will be excreted by the kidney to maintain balance. During growth, the need for positive calcium balance is substantial, and up to 400 mg of calcium/day can be deposited in the growing human skeleton. The level of ionized calcium in blood is tightly controlled despite a wide range of calcium influx from the intestine and bone. This tight control depends in a major way on the parathyroid glands that monitor plasma calcium and increase secretion of parathyroid hormone (PTH) in response to decreases in ionized calcium (Figure 2). This increase in PTH stimulates bone resorption resulting in the release of calcium and phosphorus. PTH acts upon the kidney to increase the reabsorption of calcium and stimulates production of calcitriol, which then increases intestinal calcium and phosphorus absorption. The increased influx of phosphorus from the intestine and bone is excreted by the actions of PTH upon the kidney, thereby restoring homeostasis.

The nature of the calcium sensing by the parathyroid gland has been recently elucidated following the cloning of a G protein-coupled, calcium-sensing receptor from bovine [2] and human [3] parathyroid glands, and rat [4] and human kidney [5]. The deduced amino acid sequence of this receptor shows the characteristic 7-membrane-spanning signature found in all G protein-coupled receptors, and it has some amino acid similarity to the metabotropic glutamate receptors in the central nervous system (CNS). A variety of cells can directly recognize and respond to small changes in their ambient calcium level through this receptor, and it may mediate several of the known effects of calcium on parathyroid and renal function. The physiological relevance of this receptor in calcium homeostasis in man has been demonstrated by the identification both of inactivating and activat-

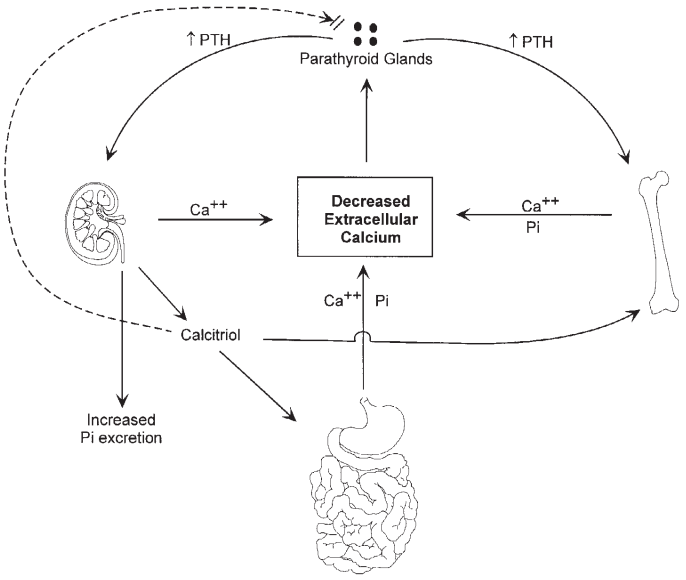

Figure 2. Parathyroid gland response to decreases in ionized calcium.

ing mutations in this calcium-sensing receptor, which result in hypercalcemic (familial hypocalciuric hypercalcemia) and hypocalcemic (neonatal severe hypocalcemia and autosomal dominant hypocalcemia) phenotypes, respectively [6, 7].

Intestinal Calcium Absorption

Net intestinal absorption averages 25 – 30% of a normal dietary intake [1]. The efficiency of intestinal absorption increases as dietary calcium is reduced, so that neutral calcium balance can be maintained at intakes as low as 150 mg/day. The efficiency of absorption normally increases during periods of increased skeletal mineralization, such as growth and pregnancy, and with administration of vitamin D metabolites. Intestinal absorption declines with age, during vitamin D depletion, and during increased intake of oxalate and phytic acid (abundant in many plant tissues).

Regulation of Calcium Absorption

Absorption of calcium across the intestinal mucosa is achieved by 2 processes that occur in tandem: an active transcellular transport (saturable and energy-requiring) and a passive paracellular diffusion process (nonsaturable) [1]. The duodenum is the major site of the active transport process, while the passive mechanism occurs throughout the small intestine and the colon. The absorption rate in all intestinal segments is increased by vitamin D, with the duodenum being the most responsive.

The active mechanism involves transport across the apical membrane, transport across the cytosol, and extrusion across the basolateral membrane. The initial entry involves calcium channels. Within the cell, calcium is bound to a calcium-binding protein, calbindin, which probably protects against toxic increases in cytosolic calcium and transports the calcium across the cell to the basolateral membrane. An ATP-dependent calcium pump in the basolateral membrane that has a higher

affinity for calcium than calbindin is responsible for the extrusion of calcium from the cell. The regulation of calbindin and the plasma membrane calcium pump is vitamin D dependent [8]. This active component becomes saturated at relatively low calcium intake (< 500 mg/day). When daily calcium intake exceeds 500 mg, passive paracellular absorption occurs, which depends on and varies linearly with intestinal calcium concentration and is driven by electrical and chemical gradients. It is nonsaturable; however, there is a possibility that tight junction mediated calcium transport may also be regulated by calcitriol.

The major regulator of intestinal calcium absorption is calcitriol which acts through genomic and nongenomic mechanisms. The genomic mechanism is analogous to that of other steroid hormones in that the ligand, calcitriol, binds to the vitamin D receptor (VDR). Calcitriol regulates the transcription of many genes including that for VDR, calbindin, and the plasma membrane calcium pump. Following administration of calcitriol, there are increases in VDR, calbindin and calcium pump, which correspond to an increase in calcium transport. In addition, there is strong evidence for a rapid nongenomic effect of calcitriol on calcium absorption (transcaltachia) that is independent of the requirement for gene transcription. This effect occurs very rapidly, within seconds to minutes, and is too rapid to be the result of gene transcription [9].

While vitamin D is the most important systemic factor involved in the regulation of calcium absorption, a variety of other factors may also play a role. Many of these factors, such as PTH, growth hormone, estrogen, and loop diuretics, increase intestinal absorption indirectly by increasing the synthesis of calcitriol. On the other hand, glucocorticoids, metabolic acidosis, and thiazide diuretics may decrease intestinal calcium absorption. Other substances within the intestinal lumen, such as phosphate, oxalate, long chain fatty acids, and fiber, decrease calcium absorption. Conversely, lysine, arginine, and lactose increase calcium absorption [10].

Renal Handling of Calcium

To maintain balance, the kidney needs to excrete an amount of calcium which is equal to the daily net intestinal calcium absorption (approximately 200 mg). Renal excretion of calcium begins with the filtration of the ultrafiltrable fraction of plasma calcium (UFCa). This and the glomerular filtration rate (GFR × UFCa) comprise the filtered load of approximately 9,000 mg/day. Therefore, 98 – 99% (8,800 mg/day) needs to be reabsorbed to allow the excretion of 200 mg/day, which is required to maintain balance. Approximately 70% of filtered calcium is reabsorbed in the proximal convoluted tubule (PCT), 20% in the thick ascending limb of the loop of Henle, 5 – 10% in the distal tubule, and < 4% in the collecting tubule. Transcellular transport across the renal tubular cell resembles that which occurs in enterocytes [1]. As in the intestine, a large proportion of the transport occurs via the paracellular pathway.

In the PCT, reabsorption of calcium is largely passive and is proportional to sodium and water reabsorption [11]. Reabsorption is enhanced by extracellular fluid (ECF) volume contraction and is diminished by ECF volume expansion. In the proximal straight tubule, calcium is transported against both electrical and chemical gradients, suggesting that the transport process is energy-requiring, active, and dissociable from sodium and water transport [12]. Most studies show that reabsorption of calcium in the medullary portion of the thick ascending loop of Henle is passive,

driven by the positive luminal potential, which depends on the activity of the Na-K-2Cl transporter. Hormonal regulation may also occur in this segment.

In the distal convoluted tubule (DCT), only 5 – 10% of calcium reabsorption occurs. The transport process is active, occurring against an electrochemical gradient, and it can be dissociated from sodium reabsorption by administering a thiazide. PTH also enhances calcium reabsorption independent of changes in sodium reabsorption or luminal potential, possibly by stimulating adenylate cyclase in the granular cells [13]. Less than 4% of calcium reabsorption occurs in the collecting duct. Current evidence suggests that the reabsorption process is active, occurring in the granular cortical collecting tubule and is independent of electrical potential or sodium transport [13]. This part of the nephron may play a role in the final regulation of renal calcium reabsorption.

Regulation of Calcium Excretion by the Kidney

Much of the regulation of calcium excretion occurs in the distal tubule where the effects of calciotropic hormones on calcium transport are localized. In general, the process appears to be similar to calcium transport in the enterocyte. A variety of factors may influence the renal handling of calcium [1].

A high intake of dietary calcium will increase urinary calcium excretion, both by increasing the filtered load, if serum calcium increases, and by suppressing PTH. Conversely, phosphate administration tends to decrease urinary calcium excretion by decreasing the filtered load of calcium and by stimulating PTH secretion.

PTH is thought to be the primary homeostatic regulator of renal calcium excretion and serves to increase calcium reabsorption by the kidney; however, increases in serum calcium as a result of the actions of PTH on bone may override this effect so that frank hypercalciuria may occur. Also, PTH has been shown to reduce GFR by altering the K_f of the glomerular capillaries [1]. This reduction in the filtered load of calcium, along with the enhancement of tubule reabsorption, results in decreased calcium excretion. The effects of calcitriol on renal calcium excretion remain ill-defined. It is likely, however, that the direct effect of calcitriol is to increase urinary calcium excretion independent of the changes in PTH and serum calcium.

In general, acidosis is associated with increases in urinary calcium by increasing the release of calcium from bone and by inhibiting tubular calcium reabsorption. Acidosis also increases the proportion of ultrafiltrable calcium by decreasing calcium binding to serum proteins. Alkalosis, on the other hand, tends to reduce urinary calcium by increasing calcium binding to proteins, therefore decreasing free calcium levels and increasing PTH secretion. It has also been shown that alkalosis enhances renal tubular calcium reabsorption independent of any change in PTH. Hypercalcemia of any cause leads to hypercalciuria, especially if PTH secretion is suppressed. Loop diuretics increase calcium excretion by decreasing calcium reabsorption in the loop of Henle. Thiazide diuretics, on the other hand, decrease calcium excretion. Glucose infusion enhances calcium excretion by decreasing calcium reabsorption in the proximal tubule. Insulin infusion and hyperinsulinemia are also associated with hypercalciuria.

Abnormalities in the recently described calcium receptor may also be associated with alterations in calcium excretion such as those found in patients with familial hypocalciuric hypercalcemia [6].

Calcium Metabolism in Bone

Under normal circumstances, there is constant mobilization of calcium from bone and deposition of calcium in newly-formed osteoid as part of the continuous process of normal bone remodeling that occurs throughout life. During growth, the net effect is to deposit calcium into the growing skeleton. The converse, an excessive rate of bone resorption, can be the result of disease states in which the normal coupling between bone formation and resorption is disturbed, leading to net skeletal loss. These diseases include hyperparathyroidism, hypercalcemia of malignancy, multiple myeloma, and osteoporosis.

Several hormones are known to regulate osteocyte and osteoclast activity in bone. PTH is the major regulator of bone turnover. The target cell for PTH is the osteoblast, and effects upon osteoclasts are thought to be indirect. Although PTH stimulates both bone formation and bone resorption, the net effect of sustained increases in PTH is loss of bone. Current evidence indicates that intermittent elevations of PTH may actually be associated with a net increase in bone formation. PTH also increases the conversion of mononuclear cells to osteoclasts. Like PTH, the principal target cell for calcitriol action is the osteoblast. While calcitriol appears to be essential for normal bone growth and mineralization, its net effect on bone formation depends on the balance between the negative effect on osteoblast number and its positive effect on bone formation per osteoblast. The actions of calcitriol are complex and likely related to multiple effects on bone cells, such as enhancing mineralization of osteoid and synthesis of subcellular organelles in osteoblasts and osteocytes, as well as altering the concentration of extracellular calcium and phosphorus. Calcitriol also exerts a permissive effect on PTH-stimulated osteoclastic resorption. Bone remodeling is regulated not only by PTH and calcitriol but also by other hormones such as insulin, growth hormone, calcitonin, IGF-1, glucocorticoids, sex hormones, thyroid hormones, and a variety of locally produced cytokines. Calcitonin inhibits bone resorption and induces hypocalcemia; however, its importance in the daily physiological regulation of skeletal calcium is not known. In addition, bone resorption may be altered by hormone-independent mechanisms such as systemic acidosis, in which bone mineral is released from the skeleton to buffer hydrogen ions.

Hypocalcemia

The hormonal systems responsible for the maintenance of normal plasma calcium concentrations are made up of PTH, vitamin D, and the target organs for these hormones, i.e. bone, kidney, and intestine. Because the presence of both PTH and vitamin D is required for full expression or activity of the other, hypocalcemia may commonly result from a defect in either the PTH or vitamin D system.

The causes of hypocalcemia can be classified into the following categories (Table 1):

Decreased PTH secretion may be due to idiopathic or acquired hypoparathyroidism [14]. Idiopathic hypoparathyroidism, which is relatively rare, may be familial or sporadic and can present at any age. Surgical hypoparathyroidism may result from thyroid, parathyroid, or radical neck surgery and may be transient or permanent [15]. Hypoparathyroidism has been reported with parathyroid infiltration by malignancy, iron, copper, and possibly amyloid [16 – 19], and also following neck irradiation. Hypomagnesemia causes hypocalcemia by decreasing the release of PTH and may impair PTH-induced

Table 1. Causes of Hypocalcemia

Disorders of the parathyroid
- Decreased PTH secretion
  - – Hypoparathyroidism
  - – Idiopathic, surgical, infiltrative, radiation-induced, magnesium depletion
- PTH resistance
  - – Pseudohypoparathyroidism Type 1a, 1b, 1c, 2
  - – Magnesium depletion
  - – Renal failure

Disorders of vitamin D metabolism
- Vitamin D deficiency
  - – Dietary
  - – Malabsorption
  - – Lack of exposure to sun
- Decreased production of 25(OH)D_3
  - – Severe liver disease
- Increased metabolism of 25(OH)D_3
  - – Anticonvulsant therapy
- Decreased production of calcitriol
  - – Renal failure
  - – VDDR I
  - – Hyperphosphatemia
  - – Oncogenic osteomalacia
- Vitamin D resistance
  - – VDDR II

Relocation of circulating calcium
- Extravascular deposition
  - – Hungry bone syndrome
  - – Pancreatitis
  - – Osteoblastic metastases
- Intravascular binding
  - – Citrate, EDTA, acute respiratory alkalosis

Miscellaneous
- Sepsis
- Drugs
  - – Gentamycin, cisplatin, mithramycin, bisphosphonates, phosphate salts
- Hypoproteinemia

release of calcium from bone (see sections on phosphate and magnesium). Resistance to the actions of PTH will also result in hypocalcemia and can occur in pseudohypoparathyroidism, renal failure, and magnesium depletion (see section on phosphate).

Disorders of vitamin D metabolism will also result in hypocalcemia. Vitamin D regulates intestinal calcium absorption, skeletal responsiveness to PTH, and normal bone turnover. Thus, the pathogenesis of hypocalcemia may reflect one or more of these physiologic actions of vitamin D metabolites. Vitamin D deficiency may result from abnormalities at any point in its metabolic pathway, including diminished intake or intestinal absorption, reduced formation of the precursor in the skin, and impaired hydroxylation in the liver and kidney including hereditary deficiency of 1-α-hydroxylase (vitamin D-dependent rickets). Vitamin D resistance may also occur because of disorders of the vitamin D receptor leading to defective action on the target organs.

Relocation of circulating calcium which may occur in several clinical circumstances also causes hypocalcemia. Profound hypocalcemia associated with hypophosphatemia and hypomagnesemia may occur after surgical correction of primary or secondary hyperparathyroidism associated with severe osteitis fibrosa cystica. This condition, known as the hungry bone syndrome or recalcification tetany, results from rapid and excess bone mineralization over bone resorption [20]. The severity of hypocalcemia correlates well with the severity of bone disease before treatment. Predictors of its occurrence after surgery for primary hyperparathyroidism include more severe hypercalcemia, higher alkaline phosphatase and PTH levels, renal insufficiency, and larger parathyroid adenomas. Hypocalcemia occurs in 40 – 70% of patients with acute pancreatitis, likely due to calcium deposition in areas of fat necrosis [21]. Hyperphosphatemia may cause hypocalcemia by precipitation of calcium phosphate complexes in soft tissues and by inhibition of 1-α-hydroxylase, which results in decreased formation of 1-α,25-$(OH)_2D_3$. Inhibition of calcium re-

lease from bone by hyperphosphatemia may also contribute to hypocalcemia. Renal failure may be associated with hypocalcemia by several mechanisms, including hyperphosphatemia, impaired production of calcitriol because of the reduced renal mass, skeletal resistance to vitamin D and PTH, and metabolic acidosis.

Increased intravascular binding of calcium may also result in hypocalcemia. Infusion of citrate (given with blood transfusion) or ethylene diaminetetraacetic acid (EDTA) can chelate calcium in the blood, thereby reducing the ionized calcium concentration without affecting total calcium. A similar effect is induced by acute respiratory alkalosis, which enhances calcium binding to albumin.

Miscellaneous causes of hypocalcemia include hypoalbuminemia which results in reduced total calcium with normal ionized calcium, which alone is not clinically significant. Several drugs may be associated with hypocalcemia. The anticonvulsants phenobarbital and diphenylhydantoin cause hypocalcemia by inducing hepatic microsomal P450 oxidase activity, leading to accelerated metabolism of vitamin D_3 and $25(OH)D_3$ into polar, hydroxylated, and biologically inactive products [22]. Cisplantin causes hypocalcemia by inducing renal magnesium wasting and hypomagnesemia [23]. The incidence of hypocalcemia in the critically ill or postsurgical patient may approach 80 %. The vast majority of these cases are due to hypoalbuminemia, and the ionized calcium concentration is normal.

Clinical Manifestations of Hypocalcemia

The clinical manifestations of hypocalcemia depend partly on the underlying cause. They may be subtle (e.g. depression) or florid (e.g. tetany), and their severity is not closely related to the degree of hypocalcemia. Asymptomatic hypocalcemia may contribute to cardiac dysfunction, including hypotension and heart failure [24]. Profound hypocalcemia may not be associated with any symptoms, as in many patients with renal failure. The concurrent blood pH, as well as other electrolyte abnormalities, is likely to influence the symptoms.

– *Neuromuscular manifestations*
The classic manifestation of neuromuscular irritability in hypocalcemia is tetany. It usually begins with circumoral and acral paresthesias and may progress to the typical cramps in the muscles of the hands (main d'accoucheur, with adduction of thumbs and flexion of MCP joints), larynx (laryngismus), or elsewhere. Latent tetany may be detected by observing a facial twitch on tapping the branches of the facial nerve (Chvostek sign, present in 25% of normal adults), or by observing carpopedal spasm, which is produced after 3 minutes of inflation of a sphygmomanometer cuff above systolic pressure (Trousseau's sign, more specific, but can be negative in 30% of patients with latent tetany). Acidosis protects against tetany, while alkalosis facilitates tetany [25]. Correction of the metabolic acidosis in patients with renal failure and severe hypocalcemia may precipitate tetany. Seizures may be the presenting manifestation of hypocalcemia. Hypocalcemia may be associated with mental retardation in children and dementia in adults. The latter may improve considerably with correction of hypocalcemia. Reversible emotional instability, anxiety, confusion, hallucination, and psychosis may occur in hypocalcemia.

– *Cardiovascular, ectodermal, and gastrointestinal effects*
EKG manifestations of hypocalcemia include prolongation of the Q-T interval and nonspecific T wave changes. Coarse, dry, and scaly skin; brittle nails; and thin and sparse hair have all been observed after hypocalcemia. Children with hypoparathyroidism may exhibit dental aplasia, hypoplasia, or caries. Psoriasis and eczema can be exacerbated by hypocalcemia. Bilateral cataracts may also occur, and treatment of hypocalcemia arrests their progression.

Diagnostic Approach to Hypocalcemia

Once hypocalcemia has been found on routine laboratory testing or is suspected on a clinical basis, the initial step should be an assessment of the serum ionized calcium. Both the history and physical examination may be helpful in providing clues, such as possible surgical hypoparathyroidism, idiopathic hypoparathyroidism (e.g. candidiasis), pseudohypoparathyroidism (somatic features), vitamin D deficiency (diet and intestinal disease), and magnesium deficiency.

Determination of the PTH level helps distinguish PTH deficiency from conditions in which responsiveness to PTH is impaired. Measurement of serum vitamin D metabolite levels, especially 25(OH)D and calcitriol, may be of great value in differentiating the various forms of vitamin D deficiency and vitamin D resistance.

Treatment

Treatment of hypocalcemia depends on severity, rapidity of onset, the presence of symptoms, and the underlying cause. It should be emphasized that correction of the underlying disease is generally required for persistent normalization of the plasma calcium concentration.

Mild asymptomatic hypocalcemia (plasma ionized calcium > 3.2 mg/dL) is well tolerated and can be managed initially by increasing dietary calcium intake or by oral calcium supplements (250 to 500 mg elemental calcium every 6 hours). Symptomatic hypocalcemia should be treated as a medical emergency and requires parenteral calcium, which should be given with caution to patients receiving digitalis to prevent toxicity. Initial therapy consists of 1 – 2 ampules of calcium gluconate (90 mg of elemental calcium per 10-ml ampule) in 5 – 10 mL of 5% dextrose given over 5 – 10 minutes, repeated as needed. Slow administration is critical, because the rapid IV infusion of calcium can cause serious cardiac dysfunction, including systolic arrest. An infusion of elemental calcium at a rate of 0.5 – 1.5 mg/kg/hour should follow initial treatment. Intravenous calcium should be continued until the patient is on an effective regimen of oral calcium and vitamin D.

Hypocalcemia due to magnesium depletion requires parenteral magnesium sulfate. Hypocalcemia after parathyroidectomy may be severe and may result from the hungry bone syndrome (especially in patients with osteitis fibrosa cystica) [20]. Careful monitoring is required to prevent potentially serious complications; therefore, plasma calcium should be measured 2 – 4 times daily for the first few postoperative days. Oral calcium (2 – 4 g of elemental calcium [50 – 100 mmol]/day) should be given when the patient is able to swallow. Intravenous calcium is indicated if the patient develops tetany, latent tetany, or a plasma calcium concentration < 7.5 mg/dL (1.9 mmol/L). Massive and prolonged supplementation of calcium may generally be re-

quired (1 – 4 mg/kg/hour of elemental calcium given in 1 L of 5% dextrose, initiated at 40 – 50 mL/hour, and titrated according to the plasma calcium) to maintain the plasma calcium above 8 mg/dL. Calcitriol (oral or IV, 2.0 – 3.0 μg/day) should be initiated if the foregoing measures are not adequate. For patients on dialysis who are deemed to be at high risk for the hungry bone syndrome, IV calcitriol (2 μg at the end of each dialysis) started 3 – 5 days before parathyroidectomy and continued postoperatively may help prevent severe hypocalcemia. Management of chronic hypocalcemia in patients with relatively normal renal function requires therapy with oral calcitriol together with oral calcium supplements. Care should be taken to avoid severe hypercalciuria by maintaining serum calcium at the lower limits of normal. Thiazide diuretics with dietary salt restriction may be useful adjuncts to such therapy.

Hypercalcemia

Hypercalcemia is a relatively frequent medical problem. The prevalence and causes of hypercalcemia are distinctly different among individuals in the general population and hospitalized patients. The prevalence in the general population is up to 0.1%, but may be higher in the hospital inpatient population [26]. Among its many causes, by far the most common are malignancy and primary hyperparathyroidism, which together account for up to 80 – 90%. Among ambulatory outpatients with hypercalcemia, the vast majority have primary hyperparathyroidism, and prompt identification of hypercalcemia and its causes becomes of paramount importance in preventing the morbidity and mortality associated with this metabolic disorder.

Table 2. Causes of Hypercalcemia

Parathyroid-related
Primary hyperparathyroidism
Adenoma, hyperplasia, carcinoma
MEA
Type 1 and 2
FHH
Tertiary hyperparathyroidism
Malignancy-related
Humoral hypercalcemia of malignancy
Lung, breast, renal, esophagus, cervix, head and neck
Skeletal involvement
Myeloma, lymphoma, metastases
Vitamin D-related
Vitamin D intoxication
Granulomatous disorders
Sarcoidosis, histoplasmosis, tuberculosis
Drug-related
Lithium, thiazides, vitamin D, vitamin A, aluminum intoxication
Miscellaneous
Immobilization, postrenal transplantation, Milk alkali syndrome, hyperthyroidism, Paget's disease

The causes of hypercalcemia are shown in Table 2. Primary hyperparathyroidism may occur as often as 1 in 500 individuals and is most often benign. Approximately 85% of patients with primary hyperparathyroidism have single adenomas, 10 – 15% have diffuse hyperplasia, and < 5% have parathyroid carcinomas. The principal systems affected include the kidney, bone, CNS and gastrointestinal tract. Hypercalcemia results from increased bone resorption, increased intestinal absorption of calcium secondary to a PTH-induced increase in $1,25(OH)_2D_3$, and also to

increased renal reabsorption of calcium mediated by the increased PTH. Renal sequelae of PTH excess and hypercalcemia include nephrolithiasis (in 10 – 15% of cases), nephrocalcinosis, polyuria, dehydration, renal insufficiency, and, rarely, renal failure. Skeletal manifestations of hyperparathyroidism include diffuse osteopenia, subperiosteal bone resorption, endosteal erosion, cortical striations, osteosclerosis, "rugger jersey spine", and osteitis fibrosa cystica [27]. The latter lesion is classic for hyperparathyroidism, but is rare. Patients with significant skeletal involvement may have progressive bone pain and pathologic fractures. Gastrointestinal complications of hyperparathyroidism include peptic ulcer disease and pancreatitis. Hyperparathyroidism can also be found in patients with multiple endocrine adenomatosis (MEA). Werner's syndrome (MEA type I) consists of pancreatic and pituitary tumors associated with parathyroid adenomas. Pheochromocytomas and medullary carcinoma of the thyroid are found in MEA type II. This condition is associated with hyperparathyroidism in type II a or with mucosal neuromas in type II b. Both MEA I and II are inherited as autosomal dominant traits.

Familial hypocalciuric hypercalcemia (FHH) is characterized by hypercalcemia beginning in the first decade of life, low fractional urinary calcium excretion (a value < than 0.01 suggests FHH is present), a tendency to develop hypermagnesemia, normal renal function, and failure of hypercalcemia to be corrected by subtotal parathyroidectomy [28]. It is inherited as autosomal dominant trait. Whereas chronic hypercalcemia in primary hyperparathyroidism is associated with severe impairment in urine concentrating ability, patients with FHH and long-standing hypercalcemia do not display such an impairment [29]. The FHH gene has been localized to the long arm of chromosome 3. Recently, as described above, the gene encoding the calcium receptor, which is highly expressed in the kidney and parathyroid gland and functions to sense physiologically relevant changes in serum calcium, was localized to the FHH locus on chromosome 3, and mutations in this gene explain this syndrome [6]. The lack of defective urinary concentration in FHH patients is likely explained by the effects of the calcium-sensing receptor on the function of the thick ascending loop of Henle, and on water reabsorption in the collecting duct [30].

Malignancy-associated hypercalcemia is the most common paraneoplastic syndrome, occurring in up to 10% of all patients with cancer [31]. Of all patients with hypercalcemia and malignancy, 44% have hematologic and 41% have solid neoplasms. Hypercalcemia complicates 11% of all the hematologic neoplasms, but only 6% of patients with solid neoplasms are hypercalcemic [32]. The most common malignancies associated with this disorder are breast, renal cell, and lung cancers along with multiple myeloma and squamous cell carcinomas of the head and neck [33]. The malignancy is almost never occult at the time when patients show hypercalcemia, and the occurrence of hypercalcemia is usually a poor prognostic factor. An exception to this rule is multiple myeloma, in which hypercalcemia may be the presenting symptom of the disease and the course may be more chronic [34]. The mechanisms responsible for the hypercalcemia are both humoral and local, and include production of a parathyroid hormone-related protein (PTHrP) by tumor cells and release of bone resorbing cytokines and growth factors by tumor cells metastatic to bone with resultant osteolysis [31]. Ectopic production of authentic PTH by tumor cells, which is extremely rare, has been documented for small cell lung cancer, ovarian cancer, and a primitive neuroectodermal cancer with extensive metastasis [35]. Pa-

tients with multiple myeloma have cystic bone lesions. The mediators of increased osteoclastic bone resorption in multiple myeloma include the interleukins IL-2 and IL-6, and tumor necrosis factor (TNF).

Vitamin D-related hypercalcemia is due to increased intestinal absorption of calcium and to increased bone resorption and can be produced with the administration of large doses of vitamin D or any of its metabolites. Sarcoidosis and other granulomatous disorders are significant causes of hypercalcemia. Hypercalciuria is a common feature of sarcoidosis (35 – 40% of unselected patients), while the incidence of hypercalcemia ranges from 2 – 25% in several studies [36]. The abnormal calcium metabolism in sarcoidosis may be the result of either excessive endogenous production or an abnormal sensitivity to calcitriol, and both sun exposure and vitamin D therapy have provoked frank hypercalcemia in affected patients [37]. Other renal complications in these patients include nephrocalcinosis and nephrolithiasis. Renal involvement in sarcoidosis can progress to acute and chronic renal failure (coexisting hypercalcemia may accelerate development of the latter). Typically, patients with hypercalcemia have elevated levels of $1,25(OH)_2$ vitamin D and suppressed PTH levels [36]. The elevated plasma levels of $1,25(OH)_2D_3$ in sarcoidosis result from its increased production by the macrophage, a prominent constituent of the sarcoid granuloma that possesses $25(OH)D_3$-1-α-hydroxylase [38]. The 1-α-hydroxylation reaction in macrophages is inhibited by glucocorticoids, and this explains in part why these agents are the mainstay of therapy of sarcoid-induced hypercalcemia [39]. Other granulomatous disorders associated with hypercalcemia include tuberculosis, histoplasmosis, coccidiomycosis, berylliosis, and leprosy. Evidence suggests that the pathogenetic mechanism is similar to that in sarcoidosis.

Drug therapy, including vitamin D and vitamin A therapy, must also be considered in the differential diagnosis of hypercalcemia. Thiazide diuretics can be associated with hypercalcemia, particularly when an underlying condition may perpetuate the increase in serum calcium. The mechanisms include a thiazide-induced volume contraction that may increase renal reabsorption of calcium, and contraction metabolic alkalosis that may lead to increased calcium binding by proteins. A direct effect of thiazides on distal tubular calcium reabsorption has been shown in the rat, and, a direct effect of thiazides on bone has been shown in dogs [40]. The latter finding is supported by the thiazide-induced hypercalcemia observed in hemodialysis patients. Lithium therapy has been reported to result in hypercalcemia with high levels of circulating immunoreactive PTH levels [41]. Lithium may increase the threshold at which serum calcium suppresses PTH secretion. Also, lithium carbonate can produce hypocalciuria, probably mediated in part by excess PTH secretion or direct enhancement of tubular calcium reabsorption. Calcium carbonate and acetate therapy in large doses, used as phosphate binders in patients undergoing dialysis, can lead to hypercalcemia. This tendency is accelerated in patients undergoing dialysis who have aluminum-induced low-turnover bone disease. Hypercalcemia can occur in these patients with or without the concomitant administration of calcitriol.

Additional causes of hypercalcemia include immobilization, especially in children, and Paget's disease patients in whom bone turnover is increased [42]. Hyperthyroidism may also be associated with hypercalcemia. Post-transplantation hypercalcemia with elevated serum PTH after successful renal transplantation can occur in 8 – 35% of cases [43]. Typically, hypercalcemia disappears within 6 months after transplantation but may last as

long as 24 months. Other contributing factors include osteomalacia, phosphate depletion, and the use of steroids and diuretics. The milk-alkali syndrome is characterized by hypercalcemia, metabolic alkalosis, and renal insufficiency. Hypercalcemia is caused by the ingestion of large quantities of calcium, which leads to increased serum calcium, together with the ingestion of alkali, which increases protein-bound calcium and renal reabsorption of calcium. Hyperphosphatemia may develop in this syndrome because of either the high phosphate content of milk or the concomitant renal insufficiency. The combination of hypercalcemia and hyperphosphatemia in the face of metabolic alkalosis may produce metastatic calcification and further renal damage. Dietary modifications are an essential part of therapy for this syndrome.

Consequences of Hypercalcemia

The clinical manifestations of hypercalcemia are influenced by the degree of hypercalcemia and the rate of onset. The clinical spectrum of hypercalcemia ranges from the asymptomatic patient found on a routine serum analysis to the patient with hypercalcemic crisis who presents in coma. The clinical manifestations of hypercalcemia reflect disturbances in gastrointestinal, cardiovascular, renal, and CNS function. CNS manifestations can range from subtle alterations in personality to acute psychosis. Specific manifestations include depression, bizarre behavior, apathy, drowsiness, memory impairment, obtundation, or even coma. Increased calcium in cerebrospinal fluid has been alleged to decrease the conduction of nerve terminals. Cardiovascular manifestations of hypercalcemia reflect the fact that calcium is an important regulator of excitation-contraction coupling of the heart and of smooth muscle tension in peripheral vessels. It exerts a positive inotropic effect on the heart and reduces heart rate, similar to the effect of cardiac glycosides. Hypercalcemia causes shortening of the Q-T interval in the EKG. Calcification of cardiac valves and narrowing of coronary arteries as well as extensive pulmonary calcification has been reported in chronic hypercalcemia. Renal manifestations include impairment of renal function as a result of decreased renal blood flow (RBF) and GFR. Impairment of sodium reabsorption, which results from inhibition of Na^+-K^+-ATPase in the thick ascending limb and distal tubules, leads to volume contraction in hypercalcemia [44]. Polyuria results from impairment of the renal concentration capacity, which may be mediated by the calcium-sensing receptor [30]. Calcium nephropathy, which presents clinically as interstitial nephritis, results from calcium deposition and interstitial inflammation.

Gastrointestinal manifestations include constipation, nausea, vomiting, and anorexia. Duodenal ulcer disease occurs in 10 – 20% of patients with hypercalcemia. Pancreatitis can occur in as many as 35% of patients in acute hypercalcemic crisis. Metastatic calcification of soft tissue may give rise to nephrocalcinosis and calcification of pancreatic ducts, gastric mucosa, intima or media of blood vessels, joint cartilage (chondrocalcinosis), cornea and conjunctiva (band keratopathy), skin, heart, lung, or other locations.

Diagnostic Approach to Hypercalcemia

Several principles guide the approach to the hypercalcemic patient. First, a PTH level elevated above the normal range in a patient with hypercalcemia is almost always indicative of primary hyperparathyroidism. Second, the number of patients with malignancy and ele-

vated PTH caused by ectopic production of authentic PTH is exceedingly small and is far fewer than the number of patients with coexistent malignancy and hyperparathyroidism. Third, malignancy-associated hypercalcemia is rarely the only manifestation of underlying malignancy. Fourth, the clinically asymptomatic patient with hypercalcemia detected by an autoanalyzer will almost always have primary hyperparathyroidism. Vitamin D or A intoxication, granulomatous diseases, milk-alkali syndrome, and other causes for hypercalcemia are usually obvious by initial history and physical examination.

With these principles in mind, the following approach is suggested. All patients with hypercalcemia should undergo a complete history and physical and routine laboratory studies including radiography of the chest and urinalysis. Any abnormality or organ-specific symptom complex should be further evaluated to rule out the presence of malignancy. In the absence of detectable malignancy, a PTH level should be obtained. A distinctly elevated midregion or intact PTH should be considered as evidence of primary hyperparathyroidism. If the PTH level is within the normal range, the diagnosis could still be hyperparathyroidism, but other known causes of hypercalcemia should be reviewed and other diagnostic tests considered based on suggestive clues in the history and physical. A urine calcium-to-creatinine ratio should be obtained to rule out familial hypocalciuric hypercalcemia. The presence of osteitis fibrosa, albeit rare, indicates hyperparathyroidism. An elevated level of 25(OH) vitamin D indicates vitamin D intoxication. In hypercalcemic patients without symptoms and with a normal serum PTH level and normal laboratory evaluation, the approach should be careful follow-up with repeated PTH measurements. If the PTH level is low and malignancy is not evident, and milk-alkali syndrome and vitamin D intoxication are unlikely because of history and physical exam, granulomatous diseases should be considered. Elevated angiotensin-converting enzyme and $1,25(OH)_2$ vitamin D levels and suppression of the hypercalcemia with steroids support the diagnosis of sarcoidosis.

Treatment of Hypercalcemia

The magnitude of the hypercalcemia is a key consideration in determining the need for immediate, aggressive therapy. On the basis of the serum calcium concentration alone, hypercalcemia may be classified as mild (< 12 mg/dL) moderate (12 – 15 mg/dL) or severe (> 15 mg/dL). In moderate and severe hypercalcemia, the serum calcium must be reduced expeditiously yet safely while diagnostic efforts are in progress and in preparation for definitive therapy. There are 4 basic goals for the therapy of hypercalcemia: 1) to correct dehydration, 2) to enhance the renal excretion of calcium, 3) to inhibit accelerated bone resorption, and 4) to treat the underlying disorder.

General measures include the intravenous administration of isotonic saline as the first step in the management of severe hypercalcemia. When the depleted intravascular volume is restored to normal, the serum calcium concentration should decline, at least by the degree to which dehydration raised it. The reduction usually amounts to 0.40 – 0.60 mmol/L (1.6 – 2.4 mg/dL), but hydration alone rarely leads to normalization of the serum calcium concentration in patients with severe hypercalcemia. The expansion of intravascular volume is also helpful because it increases renal calcium clearance by several mechanisms. First, the increase in the GFR leads to increased filtration of calcium. Second, proximal tubular sodium and calcium reabsorption decreases as the GFR increases.

Third, as more sodium and water are presented to distal renal tubular sites, an obligatory calciuresis ensues. The rate of saline administration should be based on the severity of the hypercalcemia, the extent of dehydration, and the tolerance of the cardiovascular system for volume expansion. A widely used regimen is to administer 2.5 – 4 L of isotonic saline daily, recognizing the need to adjust the rate of fluid administration or to administer a diuretic agent if symptoms and signs of fluid overload appear. Intake should be greater than output by at least 2 L in the first 24 hours.

In addition to hydration with saline, adjunctive therapy with a loop diuretic may be indicated to facilitate urinary excretion of calcium. Loop diuretics enhance the calciuric effects of volume expansion by inhibiting calcium reabsorption in the thick ascending limb of the loop of Henle. Thiazide diuretics should never be used in this situation because they enhance distal tubular reabsorption of calcium and thus may actually exacerbate hypercalcemia. Volume expansion must precede the administration of furosemide, because the effect of the drug depends on the delivery of calcium to the ascending limb. Intensive administration of furosemide (40 – 80 mg intravenously every 1 – 2 hours) with fluid and electrolyte replacement based on urinary losses is an effective regimen for the treatment of hypercalcemia. This aggressive approach will lead to marked hypercalciuria, but it requires frequent measurement of water and electrolyte excretion.

Four agents lower plasma calcium concentration by blocking osteoclast function: calcitonin, bisphosphonates, mithramycin, and gallium nitrate. Salmon calcitonin decreases serum calcium, predominantly by reducing bone resorption and less importantly by enhancing urinary calcium excretion. It can be given intramuscularly or subcutaneously in a dose of 4 – 8 U/kg twice a day. It is safe and nontoxic and when effective, works very rapidly to lower the plasma calcium concentration by a maximum of 1 – 2 mg/dL beginning within 2 – 3 hours [45]. Rapid loss of the effect of calcitonin can occur after 24 – 72 hours of treatment. This abolition of hypocalcemic action has been referred to as the "escape" phenomenon, which can be partly explained by down-regulation of hormone receptors, as well as by uncoupling of receptors from adenylate cyclase.

Mithramycin inhibits DNA-dependent RNA synthesis in osteoclasis. A dose of 25 μg/kg of body weight is infused in D5W over a period of 4 – 8 hours. The plasma calcium concentration begins to fall within about 12 hours and usually reaches a nadir by 48 hours. The hypocalcemic effect lasts for several days with repeated doses given at 3 – 7 day intervals [46]. Side effects include nausea, vomiting, anorexia, bone marrow suppression, and a bleeding phenomenon attributable to thrombocytopenia or decreased platelet function. Hepatoxicity and nephrotoxicity can also occur and toxicity is more likely to occur in patients with renal insufficiency because its excretion is largely renal. For these reasons, it is reserved for patients with severe malignancy-associated hypercalcemia who do not respond to other modalities, including a bisphosphonate.

Bisphosphonates are synthetic analogues of pyrophosphate not rapidly hydrolyzed in vivo. Their great affinity for bone and resistance to degradation account for their extremely long half-life in bone. They are excreted unchanged by the kidney. Their absorption from the gastrointestinal tract is generally poor, averaging < 10%, particularly when given with food. These agents inhibit osteoclastic bone resorption and retard (in a dose-dependent manner) the deposition of hydroxyapatite in bone collagen thereby increasing unmineralized osteoid and inhibiting

the formation of calcium phosphate crystals at higher doses. They are relatively nontoxic and are very useful in the management of moderately severe hypercalcemia [47]. The maximum effect is usually not seen for several days, so these agents are usually given with more rapidly acting modalities such as saline and calcitonin. Rarely, a significant response and even hypocalcemia can be seen within the first 24 hours. The bisphosphonates available in the United States are etidronate, pamidronate, and alendronate. Other bisphosphonates currently being developed or in the process of getting FDA approval, include ibandronate, tiludronate, and residronate. Pamidronate is more potent than etidronate and may produce a longer hypocalcemic response; it is probably the bisphosphonate of choice [47]. The usual IV dose varies with the degree of hypercalcemia. Up to 90 mg may be given usually as a single IV infusion over 4 or 24 hours, both of which appear to be equally effective. An oral regimen of 1200 mg daily for up to 5 days is also available. The dose should not be repeated until after a minimum of 7 days. This regimen is well tolerated and has minimal adverse effects, which include a mild transient fever, transient leukopenia, and a small reduction in serum phosphate levels.

Gallium nitrate is also useful for parenteral therapy of hypercalcemia. It appears to inhibit bone resorption by adsorbing to and reducing the solubility of hydroxyapatite crystals [48]. It has an additional effect of inhibiting PTH secretion in vitro; it may therefore be particularly effective in the treatment of hypercalcemia resulting from hyperparathyroidism. It is administered as a continuous IV infusion (200 mg/m^2 of BSA in 1 L of fluid daily for 5 days).

Because enhanced absorption of dietary calcium is primarily responsible for the hypercalcemia associated with excess vitamin D administration or with the endogenous overproduction of calcitriol, such as is seen in chronic granulomatous diseases and in occasional cases of malignant lymphoma, dietary calcium should be restricted in these cases. Glucocorticoids may also inhibit intestinal calcium absorption. The effect of steroids in the hypercalcemia of malignancy (usually hematologic) may be mediated through inhibition of osteoclastic bone reabsorption, cytolysis of tumor cells, and inhibition of prostaglandin synthesis.

Oral phosphate can decrease intestinal calcium absorption by forming insoluble calcium phosphate complexes both in the intestine and also in the plasma, thereby lowering the plasma calcium concentration. The risk of tissue calcium phosphate deposition, appears to be a limiting factor for the use of oral phosphate. This is a major concern with the use of IV phosphate, which is used only for severe, life-threatening hypercalcemia for which all other measures have failed, The usual dose is 250 mg qid, which can be increased to 500 mg qid, if severe diarrhea does not develop.

Chelation of ionized calcium using EDTA or IV phosphate has the advantage of almost immediate onset of action. However, toxicity limits the use of these agents to life-threatening refractory hypercalcemia. EDTA can cause acute renal failure (ARF), while phosphate therapy may lead to calcium phosphate precipitation in the tissues, potentially causing acute or chronic renal failure, vascular calcifications, and occasionally life-threatening arrhythmias. Hemodialysis with low or zero calcium dialysate and peritoneal dialysis (although slower) are both very effective modes of therapy. Dialysis is particularly useful in patients with renal insufficiency or congestive heart failure who cannot safely be given a saline load. However, rebound hypercalcemia may occur rapidly after cessation of therapy. Hemodialysis is the most effective

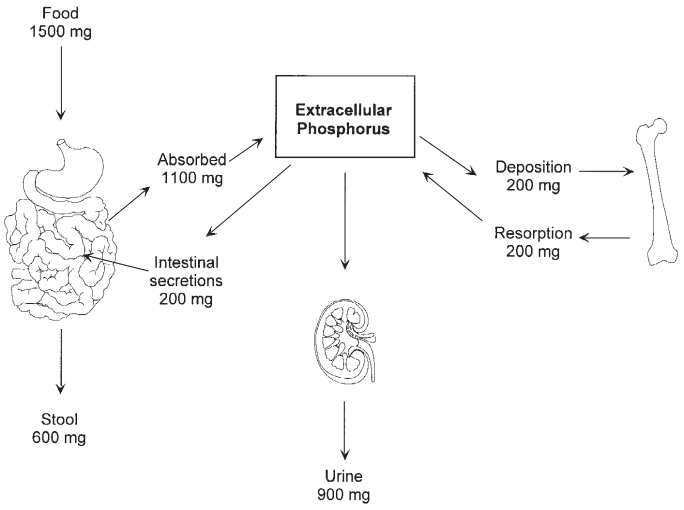

Figure 3. Normal phosphate homeostasis.

therapy for patients with severe hypercalcemia in the presence of end-stage renal disease (ESRD). Hourly removal of calcium is approximately twice that reported with saline and furosemide. It is advisable to perform hemodialysis under cardiac monitoring when using zero or low calcium dialysate.

Phosphorus

Normal Phosphate Homeostasis

The normal human body contains approximately 700 g, of phosphorus, of which 85% is contained within the bone mineral, 14% is present within the cells, and 1% is in the extracellular fluid [49, 50]. Most intracellular phosphorus is present as organic phosphate compounds which are necessary for the maintenance of cellular integrity and metabolism. Although the amount of inorganic phosphate in the cell is relatively small, it plays a critical role in cellular function because it constitutes a major source of phosphorus for the synthesis of ATP.

Plasma phosphorus concentration in adults is maintained between 2.5 and 4.5 mg/dL. The kidney and the gastrointestinal tract are the 2 major organ systems involved in maintaining phosphorus homeostasis. While phosphate absorption by the intestine may intermittently provide the extracellular fluid with a phosphate load, the kidney continuously maintains phosphate homeostasis by excreting the precise amount absorbed in excess of the body requirements. In the steady state, urinary phosphate excretion reflects the amount of phosphate absorbed by the intestine. As shown in Figure 3, the average daily intake of phosphorus is 1,500 mg, of which two-thirds is absorbed mainly in the duodenum and jejunum, and one-third is excreted in the stool. Intestinal secretions contain approximately 200 mg of phosphorus that re-enters the intestinal lumen. Approximately 200 mg of phosphorus enters and leaves the bone each day. Thus, the net intestinal absorption of phosphate is approximately 900 mg, which is excreted by the kidneys.

Intestinal Phosphate Transport

The majority of phosphate absorption takes place in the duodenum and jejunum, although the ileum and colon can absorb smaller amounts of phosphate. In normal individuals, there is a linear relationship between net phosphate absorption and dietary phosphorus intake. Intestinal phosphate absorption takes place via 2 mechanisms: 1) a diffusional process via the paracellular pathway and 2) a cellularly mediated active transport. Under normal circumstances, intestinal phosphate absorption occurs almost entirely through the diffusional process, which explains the observation that net phosphate absorption in humans is a linear function of dietary phosphate intake. Thus, the fractional absorption of phosphate from the intestine remains constant over a wide range of phosphate intake. The active component is likely to play an important role only under extreme circumstances such as severe dietary phosphate deprivation [49].

The cellularly-mediated active transport of phosphate involves sodium-dependent entry through a sodium-phosphate cotransporter in the brush border membrane. The active component of phosphate absorption is regulated by a variety of hormonal and non-hormonal factors including calcitriol. Although calcitriol increases both calcium and phosphate absorption in the intestine, different cellular mechanisms are involved in each case; thus, intestinal phosphate absorption is not necessarily coupled with calcium absorption. Other hormones that may enhance intestinal absorption of phosphate include PTH, thyroxine, estrogens, growth hormone, calcitonin, and glucocorticoids. PTH and estrogens may act mostly by increasing the synthesis of calcitriol. The mechanisms by which the other hormones affect phosphate absorption remain unclear. Nonhormonal factors may also regulate active phosphate transport. Variations in dietary phosphate intake can alter sodium-dependent phosphate transport; however, this effect is likely mediated by changes in calcitriol levels resulting from the effects of phosphorus on 1-α–hydroxylase in the kidney. The presence of aluminum in the intestinal lumen decreases phosphate absorption. Likewise, calcium-rich diets will impair phosphate uptake by the intestine.

Renal Handling of Phosphate

As already discussed, the kidney is the principal organ involved in the regulation of phosphate homeostasis. Most circulating inorganic phosphorus is ultrafiltrable. Factors that alter urinary phosphate excretion do so by changing either the filtered load or the tubular reabsorption of phosphate, because little phosphate is secreted by the kidney. Approximately 80% of the filtered load is reabsorbed by the renal tubules. Tubular reabsorption of phosphate and its regulation are determined by specific cellular events localized mostly in the proximal tubule, where 60 – 70% of renal reabsorption of phosphate takes place. Significant phosphate reabsorption occurs between the early distal tubule and the final urine. Although little is known about the mechanisms involved, there is evidence for regulated phosphate reabsorption in the distal nephron [49, 50].

– *Cellular mechanisms for proximal tubular phosphate transport*
  The transport of phosphorus in the proximal tubule is largely transcellular. It involves uptake across the brush border membrane, translocation across the cell, and efflux across the basolateral membrane. The uptake of phosphorus across

the brush border membrane is mediated by the sodium phosphate cotransporter and depends on the sodium gradient maintained by the basolateral Na-K-ATPase. Much has been learned about the nature of the sodium-phosphate (NaPi) cotransporter following its cloning in several species [51]. Once inside the cell, phosphorus may be incorporated into several organic compounds or extruded at the basolateral membrane. Little is known about the mechanisms involved in phosphate transport across the cell. At the basolateral membrane, the electrochemical gradient favors the extrusion of phosphate; however, diffusion across the basolateral membrane is limited to avoid depletion of cytosolic phosphate. Phosphate transport across the basolateral membrane appears to occur primarily by sodium-independent anion exchange mechanisms, which remain poorly understood.

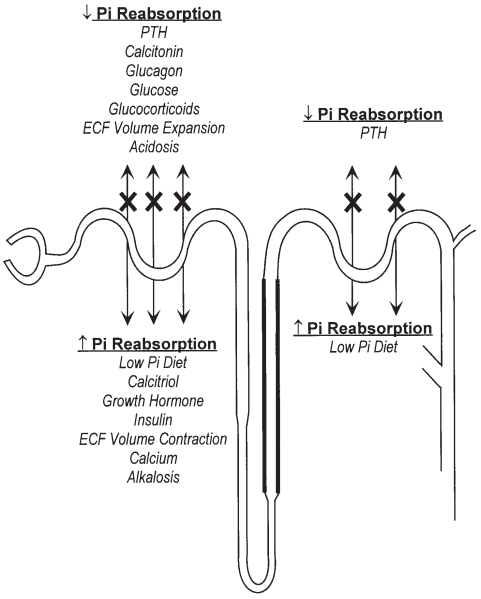

Figure 4. Tubular phosphate reabsorption.

– *Factors influencing renal handling of phosphate*

The overall tubular reabsorption of phosphate is controlled by a variety of dietary, metabolic, and hormonal factors as shown in Figure 4. Of these, PTH and dietary intake of phosphate primarily determine renal tubular phosphate reabsorption. The kidney responds to alterations in the filtered load of phosphorus by altering the excretion of phosphorus in the urine as appropriate. Urinary phosphate excretion decreases markedly in response to dietary phosphorus restriction. The adaptation of the renal tubule to dietary phosphate appears to involve alterations in Na^+-dependent phosphate transport, as suggested by studies demonstrating changes in NaPi cotransporter messenger RNA (mRNA) and protein induced by changes in dietary phosphate intake [52 – 54]. Furthermore, vitamin D metabolites may also contribute to the adaptive response to dietary phosphate restriction. The enhanced phosphate transport observed in phosphate depletion is resistant to phosphaturic agents such as PTH and calcitonin [55, 56], indicating that phosphate deprivation is a powerful stimulus for renal tubular phosphate reabsorption.

PTH is the major regulator of phosphate reabsorption by the kidney. PTH administration causes phosphaturia, and parathyroidectomy causes a decrease in urinary phosphate excretion. The primary site of action of PTH on phosphate transport is the proximal convoluted tubule and the proximal straight tubule. There is also evidence demonstrating PTH-sensitive phosphate transport in the distal nephron. The effects of PTH at the cellular

level are mediated by the PTH/PTHrP receptor located on the cell surface, which activates both adenylate cyclase and phospholipase C [57]. The effect of PTH to decrease phosphate reabsorption is thought to be largely mediated by cAMP; however, the protein kinase C pathway has also been implicated [58 – 61]. PTH has been shown to decrease NaPi cotransporters within the apical membrane resulting in decreased phosphate transport, and it has been suggested that exposure to PTH causes internalization of NaPi cotransporters by activation of endocytic mechanisms [62, 63]. The phosphaturic effect of PTH can be modified by a variety of factors. As discussed above, the increased phosphate reabsorption induced by dietary phosphate restriction can override the phosphaturic action of PTH.

Other hormones may also affect tubular phosphate reabsorption. The effect of vitamin D_3 metabolites on renal phosphate handling remains controversial. In general, acute administration of these agents is antiphosphaturic. The recent finding of vitamin D responsive elements in the Na-Pi promoter supports a direct role of vitamin D in phosphate reabsorption [64]. The antiphosphaturic effect of vitamin D may also be influenced by changes in serum calcium and PTH. Increased tubular reabsorption by growth hormone has also been recognized. Calcitonin has been shown to inhibit tubular phosphate reabsorption; however, the physiologic importance of this effect is not clear. Insulin and the insulin-like growth factors may also modulate phosphate transport. Insulin has modest antiphosphaturic effects. It has been shown to directly stimulate phosphate uptake by proximal tubules. Glucagon and glucose are both phosphaturic. The effect of glucose may be partially due to the concomitant osmotic diuresis, which inhibits proximal tubule transport. Glucocorticoids may cause phosphaturia independently of PTH. The effect of glucocortoids appears to be mediated by glucocorticoid receptors in the proximal tubule [1, 65].

Hypercalcemia has both direct and indirect effects that may contribute to increased phosphate reabsorption. The indirect effects include changes in GFR, RBF, and Kf, as well as changes in PTH levels which have profound effects on tubular phosphate handling. In addition, calcium has been shown to directly increase phosphate transport. Extracellular fluid volume expansion results in increased phosphate excretion, whereas volume contraction decreases phosphate excretion. Although the effects of volume status on tubular phosphate transport may be indirect, evidence suggests that volume expansion directly inhibits phosphate reabsorption independent of filtered load, plasma calcium, and PTH. Acid-base status can also influence renal phosphate handling. In general, acidosis is associated with decreased phosphate reabsorption, whereas alkalosis increases phosphate reabsorption; however, differences in phosphate transport also depend on whether the changes in acid-base status are acute or chronic. Diuretic agents such as acetazolamide and loop diuretics may decrease phosphate reabsorption. Phosphatonin, an as yet uncharacterized factor, has been implicated in the hyperphosphaturia of patients with X-linked hypophosphatemia and oncogenic osteomalacia [66, 67].

Hyperphosphatemia

The signs and symptoms of hyperphosphatemia are mostly related to the associated hypocalcemia and soft tissue calcification. The hypocalcemia may or may not be accompanied by tetany. Possible mechanisms for the decrease in serum calcium include deposition of calcium-phosphate salts in the soft tissues

and decreased production of calcitriol. Soft tissue calcification may occur when the calcium × phosphate product is > 70, especially in tissues with high pH, because the solubility of calcium-phosphate is lower in alkaline pH. Thus, the conjunctiva and the lung are at risk for calcium-phosphate precipitation because outward diffusion of carbon dioxide allows the local pH to increase. Consequently, band keratopathy and pulmonary calcifications may occur. ARF with intratubular precipitation of calcium and phosphorus may occur following a phosphate load. In chronic renal failure, hyperphosphatemia may lead to soft tissue calcification in the kidney, which in turn may accelerate the progression of renal failure [68]. Hyperphosphatemia plays a critical role in the development of secondary hyperparathyroidism in chronic renal failure.

Table 3. Causes of Hyperphosphatemia

Increased phosphate load	
Exogenous	
	Oral ingestion
	Vitamin D intoxication
	Intravenous administration
	Blood transfusions
	White phosphorus burns
Endogenous	
	Acidosis
	Tumor lysis syndrome
	Hemolysis
	Rhabdomyolysis
	Malignant hyperthermia
Decreased urinary excretion	
Decreased GFR	
	Acute renal failure
	Chronic renal failure
Increased tubular reabsorption	
	Hypoparathyroidism
	Pseudohypoparathyroidism
	Hyperthyroidism
	Acromegaly
	Postmenopausal state
	Glucocorticoid withdrawal
	Tumoral calcinosis
	Bisphosphonates

Causes of Hyperphosphatemia

As shown in Table 3, the causes of hyperphosphatemia can be grouped into 2 major categories: 1) increased phosphate load and 2) decreased urinary excretion. Pseudohyperphosphatemia may occur in hyperproteinemic states such as multiple myeloma, as well as in patients with hyperlipidemia, depending on the method used to measure phosphorus.

– *Increased phosphate load*
An increased phosphate load can result from either exogenous or endogenous sources. Under normal circumstances, the hyperphosphatemia is usually mild unless significant renal insufficiency or increased renal phosphate reabsorption coexist. The gastrointestinal tract is a common route of entry for exogenous phosphorus. Thus, dietary supplementation of phosphorus, particularly in combination with vitamin D, as well as phosphate-containing enemas may result in hyperphosphatemia. Likewise, hyperphosphatemia may result from the intravenous administration of phosphorus, and it usually occurs during the treatment of hypophosphatemia when the tubular reabsorptive mechanisms are adjusted to retain nearly all the filtered phosphate. Blood transfusions and infusions of lipid emulsions for total parenteral nutrition may also produce hyperphosphatemia. Phosphorus can be absorbed from the

skin, and hyperphosphatemia may develop in white phosphorus burns.

Hyperphosphatemia from endogenous sources may be caused by a shift of phosphate from intracellular stores or by a release of phosphate from the cells following tissue necrosis. Acidosis, particularly organic acidosis, may promote shifts of phosphate from the cells. The mechanism may involve the breakdown of organic phosphate with a release of inorganic phosphate into the extracellular fluid. Elevations in lactic acid are implicated in the hyperphosphatemia that may accompany major abdominal and thoracic surgery, as well as that associated with strenuous exercise. Respiratory acidosis may also lead to hyperphosphatemia. The mechanism appears to involve the decrease in intracellular pH that inhibits glycolysis, and the resultant decreased incorporation of inorganic phosphate into organic compounds leads to an increase in the efflux of phosphate from the cells.

Severe hyperphosphatemia may occur following significant tissue damage such as that seen in the tumor lysis syndrome, which occurs following chemotherapy for various malignancies, particularly lymphomas and leukemias. Acute hemolysis and rhabdomyolysis can both result in hyperphosphatemia. The hyperphosphatemia associated with malignant hyperthermia may be partially due to rhabdomyolysis.

– *Decreased urinary excretion of phosphate*

Reduced clearance of phosphorus may result from a decrease in GFR or from enhanced tubular phosphate reabsorption. Both acute and chronic renal failure can result in hyperphosphatemia. Several metabolic consequences of chronic renal failure prevent the development of significant hyperphosphatemia. These include increased PTH levels and low levels of calcitriol which decrease phosphate reabsorption. With progressive decline in GFR, however, hyperphosphatemia eventually develops.

Increased tubular reabsorption of phosphorus may occur in a variety of conditions, but it is most commonly seen in a spectrum of disorders characterized by PTH deficiency or resistance. The most common cause of hypoparathyroidism is surgical removal of the parathyroid glands, which often occurs in association with thyroid surgery, parathyroidectomy, or radical neck resections. Therapy with radioactive iodine may also result in hypoparathyroidism. Parathyroid insufficiency can also result from infiltrative processes involving the parathyroid gland, such as metastatic carcinoma and hemochromatosis. Hypoparathyroidism may be part of autoimmune endocrine failure. Hereditary hypoparathyroidism may occur in isolation or in association with Di George syndrome, characterized by defective development of the thymus, mucocutaneous candidiasis, and cardiac abnormalities.

End-organ resistance to PTH results in pseudohypoparathyroidism which involves a variety of disorders with biochemical features of hypoparathyroidism, including hyperphosphatemia and hypercalcemia, but usually with increased levels of PTH. Patients with type I pseudohypoparathyroidism (Albright hereditary osteodystrophy) have low urinary cAMP levels and phosphate excretion in response to PTH. About two-thirds of the patients with type I pseudohypoparathyroidism have somatic abnormalities as

originally described by Fuller Albright in 1942, including a short neck, round face, and shortening of the metacarpals and metatarsals. The underlying defect in type I pseudohypoparathyroidism involves the PTH receptor-cAMP generating system, and 3 types have been described: 1) type Ia is due to abnormalities of the guanine nucleotide-binding stimulatory protein [69 – 71], 2) type Ib may involve abnormalities of PTH receptor expression or function [72], and 3) type 1c is due to abnormalities of the adenylate cyclase catalytic subunit [73]. The majority of patients with somatic abnormalities have a defect in guanine nucleotide regulatory protein and, as expected, they have multiple endocrinologic defects, including hypothyroidism and gonadal dysfunction [74]. Patients with type II pseudohypoparathyroidism have high urinary cAMP but low phosphate excretion in response to PTH. Thus, in contrast to type I pseudohypoparathyroidism in which the defect is proximal to the generation of cAMP, in type II pseudohypoparathyroidism the defect is distal to the generation of cAMP. Patients with pseudohypoparathyroidism and renal tubular resistance to PTH may have normal response to the hormone at the level of the bone. Thus, these patients have somatic features of pseudohypothyroidism and hyperphosphatemia; however, they have bone changes of osteitis fibrosa.

Hyperphosphatemia may occur in association with hyperthyroidism and acromegaly. The cause of hyperphosphatemia in hyperthyroidism is likely due to a combination of factors, including increased intestinal absorption, increased bone resorption, and increased tubular reabsorption of phosphate. The mechanisms involved in the increased phosphate transport in hyperthyroidism are poorly understood. Growth hormone decreases phosphate excretion in humans. During menopause, low levels of estrogen and elevated levels of growth hormone are associated with hyperphosphatemia, which appears to result from increased tubular reabsorption of phosphate. Glucocorticoids inhibit sodium-dependent phosphate uptake by renal proximal tubular cells, and glucocorticoid withdrawal has been associated with hyperphosphatemia [75].

Tumoral calcinosis is a familial disorder associated with increased tubular reabsorption of phosphate These patients have hyperphosphatemia and calcifications in soft tissues and around large joints. PTH levels and PTH responsiveness are both normal. The exact mechanisms involved in the increased phosphate reabsorption in this syndrome are not clear. Bisphosphonate treatment of patients with Paget's disease has been associated with increased tubular reabsorption of phosphate and hyperphosphatemia [76].

Management of Hyperphosphatemia

The treatment of hyperphosphatemia should be aimed not only at the removal of phosphate from the circulation, but also at prevention [77]. Prevention includes eliminating exogenous or endogenous phosphate sources, as well as maintaining renal function. Thus, in patients receiving therapy for lymphoma who are at high risk for developing the tumor lysis syndrome, prevention of uric acid nephropathy by the administration of allopurinol and the maintenance of an alkaline diuresis may prevent severe hyperphosphatemia. Induction of an alkaline diuresis may also protect renal function and prevent severe hyperphosphatemia in patients with

rhabdomyolysis. In chronic renal failure, dietary phosphate restriction and the use of phosphate-binding antacids to impair intestinal phosphate absorption are commonly used to prevent hyperphosphatemia. In patients with severe hyperphosphatemia and dangerously elevated calcium-phosphate product, dialysis offers a means of removing phosphorus from the circulation.

Hypophosphatemia

Hypophosphatemia is a relatively common finding in hospitalized patients. A patient might have low serum levels of phosphorus with little deviation from normal in intracellular phosphorus (p-deprivation), or there might be low serum levels with low intracellular phosphorus (p-depletion). The latter represents a clinically very serious abnormality and is associated with numerous complications and organ abnormalities. In view of the important role of phosphorus as a source of energy, virtually all organ systems are affected in severe hypophosphatemia [49, 50]. Three basic underlying mechanisms affect cellular function in hypophosphatemia. First, severe hypophosphatemia results in decreased levels of erythrocyte 2,3-diphosphoglycerate (DPG), which increases the affinity of hemoglobin for oxygen, thus impairing oxygen release at the tissue level. Second, low levels of inorganic phosphate in the cell impair the synthesis of high-energy phosphate compounds such as ATP. And third, deficiency of intracellular organic phosphate may impair glycolysis. Thus, the manifestations of hypophosphatemia may involve a variety of organ systems; however, symptoms usually do not develop until the serum phosphorus level is < 1 mg/dL. Severe hypophosphatemia can affect the CNS and lead to a metabolic encephalopathy. The cardiopulmonary system can also be affected with impaired myocardial contractility leading to congestive heart failure (CHF) and weakness of the diaphragm resulting in respiratory failure. In bone, hypophosphatemia results in increased release of calcium from the bone and hypercalciuria. Prolonged hypophosphatemia may lead to a mineralization defect resulting in rickets and osteomalacia. Hypophosphatemia can affect both skeletal and smooth muscle with the latter resulting in ileus and dysphagia. Skeletal muscle dysfunction can present as a proximal myopathy or rhabdomyolysis. The hematopoietic system may also be affected by hypophosphatemia in the form of hemolysis, impaired phagocytosis and chemotactic activity, as well as thrombocytopenia.

Causes of Hypophosphatemia

As shown in Table 4, the mechanisms underlying hypophosphatemia can be grouped into three categories:

- decreased intestinal absorption of phosphorus,
- shifts of phosphorus into cells, and
- increased renal excretion of phosphate.

These mechanisms may occur singly or in combination. If none of the above mechanisms is present, pseudohypophosphatemia should be suspected, which is usually due to factors such as mannitol administration and hyperbilirubinemia that interfere with the assay used to measure serum phosphorus.

- *Decreased intestinal absorption of phosphate*
  Hypophosphatemia may occur in malnourished or starved patients who ingest

Table 4. Causes of Hypophosphatemia

Decreased intestinal absorption	
	Decreased dietary intake
	Vitamin D deficiency
	Phosphate binding antacids
	Vomiting
	Malabsorption
	Chronic alcoholism
Shift of phosphorus into cells	
	Respiratory alkalosis
	Carbohydrate load
	Nutritional recovery syndrome
	Recovery from hypothermia
	Hungry bone syndrome
Increased renal excretion	
	Hyperparathyroidism
	Malignancy
	Vitamin D deficiency
	XLH
	VDDR
	HHRH
	Idiopathic hypercalciuria
	X-linked nephrolithiasis with RF
	Fanconi syndrome
	Postrenal transplantation
	Metabolic acidosis
	Diuretics

a diet high in carbohydrates and deficient in phosphorus. Phosphorus-deficient diets are more likely to result in the development of hypophosphatemia in children than in adults. Vitamin D deficiency may lead to hypophosphatemia by decreasing intestinal phosphate absorption. Phosphate-binding antacids are used in chronic renal insufficiency and in hypoparathyroidism for the control of hyperphosphatemia, and their use may lead to hypophosphatemia. Severe vomiting and a variety of malabsorptive disorders may also lead to hypophosphatemia.

Chronic alcoholism and alcohol withdrawal are among the most common causes of severe hypophosphatemia [78]. The mechanisms involved have not been extensively studied, but it likely results from a variety of factors. Decreased intestinal absorption of phosphate because of poor dietary intake, vomiting, diarrhea, or routine use of antacids may lead to phosphate depletion. Renal losses of phosphate may result from repeated episodes of ketoacidosis with loss of phosphate from the cells into the urine; in addition, renal phosphate wasting may occur as a result of tubular dysfunction associated with alcohol. Intracellular shifts of phosphate secondary to glucose infusions or respiratory alkalosis may also contribute to hypophosphatemia in these patients.

– *Intracellular shifts of phosphate*

Inorganic phosphate is required for the synthesis of a variety of organic compounds. With stimulation of metabolic pathways, phosphate moves from the extracellular pool into the intracellular space, resulting in hypophosphatemia. One of the common causes of hypophosphatemia in the hospital setting is respiratory alkalosis due to the hyperventilation induced by a variety of factors, including pain, sepsis, depression, and alcohol withdrawal. The rise in intracellular pH in this setting results in activation of glycolysis, which increases the utilization of inorganic phosphate. Hypophosphatemia in hospitalized patients is also commonly caused by the intravenous administration of carbohydrate, usually in the form of glucose. Glucose administration may cause hypophosphatemia by increasing insulin release, which promotes phosphate uptake by the cell, and by the enhanced incorporation of phosphate into compounds involved in the glycoly-

tic pathway. The hypophosphatemia induced by glucose administration may be severe in patients with starvation. In diabetics, the decrease in serum phosphate following glucose administration is usually mild because of impaired insulin release. Fructose may cause a more severe hypophosphatemia than glucose because of its unregulated uptake by the liver [50]. The nutritional recovery syndrome occurs during the rapid refeeding of patients with starvation, and it is associated with hypophosphatemia, hypokalemia, and hypomagnesemia. Transient hypophosphatemia may occur during recovery from hypothermia because of the associated stimulation of glycolysis with rewarming. The hungry bone syndrome may occur following parathyroidectomy and is characterized by hypocalcemia and hypophosphatemia due to accelerated bone mineralization [79].

– *Increased renal excretion of phosphate*
Hyperparathyroidism causes hypophosphatemia by decreasing renal tubular reabsorption of phosphorus, as discussed earlier. Hypophosphatemia may accompany malignant neoplasms [80]. PTHrP may be produced by certain tumors and act via the PTH/PTHrP receptor in the kidney to decrease phosphate reabsorption. Some tumors of mesenchymal origin may be associated with hypophosphatemia, low levels of calcitriol and osteomalacia. These patients have normal levels of PTH and PTHrP and markedly reduced renal phosphate transport. Calcitriol administration may not improve the phosphate transport defect. Tumors associated with this syndrome are thought to secrete a phosphaturic substance that acts directly in the renal tubular cells by inhibiting sodium-dependent phosphate uptake [66].

Disorders of vitamin D metabolism, such as vitamin D deficiency and vitamin D-dependent and vitamin D-resistant rickets, are associated with decreased renal reabsorption of phosphate and hypophosphatemia. Decreased intestinal phosphate absorption may also contribute to the hypophosphatemia in these disorders. In vitamin D deficiency, the decreased tubular reabsorption of phosphate is mediated by the high levels of PTH from hypocalcemia. Vitamin D-resistant rickets or familial X-linked hypophosphatemic rickets (XLH) is similar to oncogenic osteomalacia with regard to the pathophysiologic process of hypophosphatemia. The genetic abnormality in XLH is based on mutations in the PEX gene (*p*hosphate-regulating gene with homologies to *e*ndopeptidases on the *X*-chromosome) [81]. The abnormal endopeptidase activity of the mutated gene product has been postulated to result in impaired degradation of a phosphaturic factor.

Vitamin D-dependent rickets (VDDR), also a familial disorder associated with a tubular defect in phosphate reabsorption, has been classified into types I and II. Type I VDDR is an autosomal recessive disorder that presents in early childhood with hypophosphatemia, hypocalcemia, rickets, low serum levels of calcitriol, and elevated serum levels of 25(OH)D. Patients respond to therapy with small doses of calcitriol, suggesting abnormal production of calcitriol by the kidney as the primary abnormality. Indeed, the human 1-α-hydroxylase gene has been recently found to map to the previously identified disease locus for type I VDDR, which strongly suggests that mutations of this gene are the basis for this disorder [82]. Type II VDDR is actually a form of vitamin D resistance, and it is associated with end-organ resistance to calcitriol because of mutations in the gene encoding the vitamin D receptor [83, 84]. Clinically, type

II VDDR is indistinguishable from type I VDDR except that calcitriol levels are elevated, and treatment with calcitriol is ineffective.

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is also characterized by decreased renal reabsorption of phosphate and is thought to represent a primary defect in tubular phosphate reabsorption. Idiopathic hypercalciuria may potentially represent a milder form of this disorder [85]. X-linked recessive nephrolithiasis with renal failure is a form of hereditary renal disease associated with renal phosphate wasting [86] and may represent a generalized defect in proximal tubular function. The Fanconi syndrome is a generalized impairment in proximal tubular function because of either hereditary abnormalities or acquired conditions, such as multiple myeloma. The resultant injury to the proximal tubular epithelium induces urinary losses of solutes normally reabsorbed in this nephron segment such as phosphorus, glucose, amino acids, bicarbonate and uric acid. Successful kidney transplantation may be associated with hypophosphatemia that is mostly due to a tubular phosphate leak secondary to persistent hyperparathyroidism. However, a variety of other factors may also contribute to post-transplant hypophosphatemia, including glucocorticoids, chronic volume expansion, and diuretics as well as the shift of phosphate and calcium into bone associated with the correction of hyperparathyroidism.

Metabolic acidosis decreases renal tubular reabsorption of phosphate and may cause hypophosphatemia. In addition, acidosis results in shifts of phosphate from the intracellular pool because of the breakdown of intracellular organic compounds. The released phosphate is excreted in the urine and may contribute to phosphate depletion. In diabetic ketoacidosis, the catabolic effects of insulin deficiency also contribute to the shift of phosphate into the extracellular fluid, thus worsening the phosphaturia. A variety of drugs such as thiazide diuretics and high doses of estrogen can induce renal phosphate wasting and cause hypophosphatemia.

Management of Hypophosphatemia

Patients with moderate hypophosphatemia (serum phosphorus between 1 and 2.5 mg/dL) who do not have a history of GI or renal phosphate losses rarely require phosphate replacement; rather, the treatment is aimed at the underlying cause. For example, in patients with uncomplicated diabetic ketoacidosis, the hypophosphatemia usually corrects spontaneously with normal dietary intake, and it may not be necessary to treat the hypophosphatemia per se. Likewise, patients with hypophosphatemia due to vitamin D deficiency respond to therapy with vitamin D supplementation. Phosphate supplementation, either orally or intravenously, is indicated in patients who are symptomatic; however, the latter should be reserved for patients with life-threatening complications or for those who are unable to tolerate oral feeding.

Magnesium

Normal Magnesium Homeostasis

Magnesium is the second most abundant intracellular cation. Fifty to 60% of total body magnesium is in bone, with the remainder in the soft tissues [87]. Intracellular magnesium

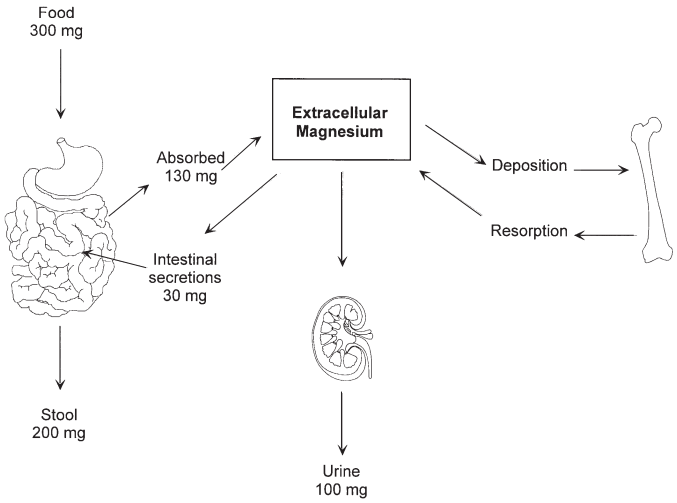

Figure 5. Normal magnesium homeostasis.

concentration is 8 – 10 mM and is mostly bound to ATP and other nucleotides and enzymes. Free magnesium concentrations are approximately 10% of total. Less than 1% of body magnesium is in the extracellular fluid and therefore, serum magnesium, like serum potassium, is not a very sensitive indicator of body stores. Serum magnesium is in 3 fractions: ionized (60%), complexed, usually with citrate or phosphate (15%) and bound to protein, mainly albumin (25%). Normal serum magnesium concentration is 1.7 – 2.3 mg/dL, of which 75% is ultrafiltrable.

Intestinal Absorption of Magnesium

The average daily intake from a variety of foods is 300 mg. As illustrated in Figure 5, approximately one-third of the ingested magnesium is absorbed, principally in the small bowel, by a saturable as well as by a passive diffusional process [88]. Some magnesium is also secreted into the intestine (approximately 30 mg). Thus, net absorption is about 100 mg. Little evidence exists for regulation of magnesium absorption in the intestine.

Renal Handling of Magnesium

In contrast to most other cations, the proximal tubule is not the major site of reabsorption of magnesium, and only 15 – 20% of filtered magnesium (ionized plus complexed) is absorbed in this segment. The major site of magnesium reabsorption is the thick ascending loop of Henle, in which 60 – 70% of the filtered magnesium is reabsorbed [89 – 91]. A large portion of the reabsorption of magnesium in this segment is by the paracellular route and is driven by the lumen positive potential resulting from the activity of the Na-K-2Cl transporter. There is also evidence that magnesium reabsorption in this segment can be regulated by hormones, e.g. PTH, suggesting additional transcellular absorption mechanisms [92].

However, hormonal effects could also be explained by alterations in sodium chloride reabsorption. Little is known about the mechanisms of magnesium reabsorption in the distal nephron, but it is believed to occur by entry through luminal magnesium channels and exit via a Na/Mg exchanger [91, 93].

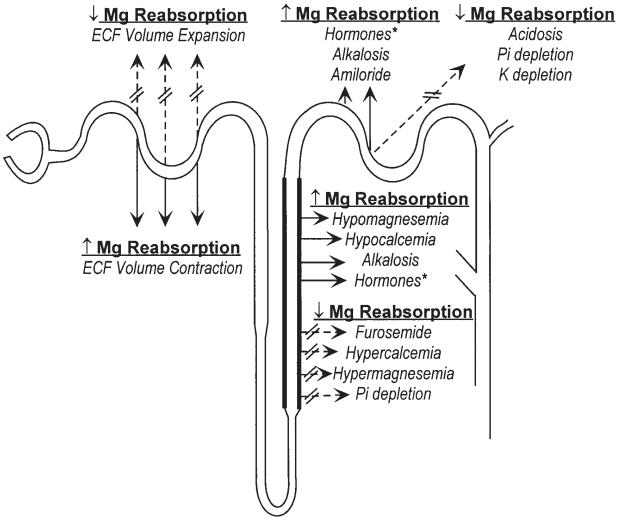

Figure 6. Factors regulating magnesium excretion
*Hormones: Parathyroid hormone, Calcitonin, Glucagon, Vasopressin.

Regulation of Magnesium Excretion

Factors regulating magnesium excretion are illustrated in Figure 6. Alteration in magnesium excretion is mainly a consequence of changes in the level of plasma magnesium, which is a potent regulator of magnesium reabsorption in the thick ascending limb [94]. Thus, hypermagnesemia decreases magnesium reabsorption, and hypomagnesemia is associated with a marked decrease in magnesium excretion. The recently described calcium-sensing receptor, which may also bind magnesium, may be involved in this regulation of magnesium reabsorption [2, 4, 95, 96]. Hypercalcemia, which inhibits magnesium reabsorption, may also affect this mechanism. Magnesium reabsorption is stimulated by PTH in this segment. Phosphate depletion [97] and systemic acidosis [98] are associated with marked hypermagnesuria. Alcohol administration, volume expansion, and glycosuria also increase magnesium excretion [99, 100]. Diuretics, both distally acting thiazides and the loop diuretics, increase magnesium excretion.

Table 5. Causes of Hypermagnesemia

Decreased renal excretion	
	Acute Renal Failure
	Chronic Renal Failure
Increased entrance to extracellular fluid	
	Magnesium-containing laxatives
	Magnesium-containing enemas
	Magnesium-containing IV fluids
	Parenteral magnesium, e.g. treatment of eclampsia

Hypermagnesemia

In normal subjects, ingested magnesium is readily excreted by the kidneys and hypermagnesemia is uncommon. Infused magnesium loads are excreted within 48 hours. Causes of hypermagnesemia are listed in Table 5. Hypermagnesemia occurs in the presence of renal failure or after large loads given by infusion or by enema. In renal failure, serum magnesium remains in the normal range until renal failure is advanced, and even

then, only modest elevations occur [101]. Severe hypermagnesemia only occurs following the injudicious ingestion or administration of magnesium-containing antacids or enemas. These should be avoided in patients with advanced renal failure. Magnesium infusions may be administered for eclampsia and usually achieve a blood concentration of 6 – 8 mg/dL. Other causes of elevations of serum magnesium are uncommon and mild.

Clinical Consequences of Hypermagnesemia

The principal manifestation of hypermagnesemia is neuromuscular toxicity shown first by decreases in reflexes (4 – 6 mg/dL) followed by somnolence and muscular paralysis, including respiratory paralysis, as magnesium rises to higher levels [102]. Hypermagnesemia acts as a calcium channel blocker in the heart and as intracellular magnesium increases, potassium channels also become blocked [103]. These effects lead to bradycardia and hypotension with abnormal ECG changes of prolonged PR interval, widened QRS, and an increase in QT interval. Complete heart block may occur, and cardiac arrest may occur at magnesium concentrations > 15 mg/dL. Elevations in magnesium can also decrease the secretion of PTH, and thus hypocalcemia may occur, but is usually transient and mild. A variety of non-specific symptoms may also occur such as nausea, vomiting, and flushing.

Hypomagnesemia

Hypomagnesemia is common in hospitalized patients (10%) and may reach 50% in patients in intensive care units [104 – 106]. The main factors involved in this setting are poor nutrition, hypoalbuminemia, and aminoglycosides. The causes of hypomagnesemia are listed in Table 6. These causes should serve to raise the awareness of potential problems in these settings and prompt the measurement of serum magnesium [107]. Decreased intake may be the cause of hypomagnesemia in protein-calorie malnutrition and in patients who have received intravenous fluids for prolonged periods. Decreases in intestinal absorption may occur with malabsorption syndromes, either from nontropical sprue or Crohn's disease or following extensive bowel resections. Biliary fistulae and prolonged nasogastric suction may also cause magnesium

Table 6. Causes of Hypomagnesemia

Decreased intake	
	Protein calorie malnutrition
	Starvation
	Prolonged intravenous fluids
Decreased intestinal absorption	
	Malabsorption syndromes
	Intestinal resection
Excess urinary losses	
	Diuretics
	Post-ATN
	Alcohol administration
	Primary aldosteronism
	Drugs : aminoglycosides, cyclosporine, cisplatin
	Phosphate depletion
	Prolonged glycosuria
	Inherited disorders of tubular transport: Bartter and Gitelman syndromes
Excess losses of body fluids	
	Prolonged NG suction
	Biliary fistula
	Severe diarrheal states
Other	
	Pancreatitis
	Blood transfusions
	Hungry bone syndrome

depletion. Urinary losses also account for a number of cases of magnesium deficiency. Diuretic therapy is often associated with hypomagnesemia, and increased renal magnesium losses occur in glycosuric states such as diabetic ketoacidosis, primary hyperaldosteronism, volume expansion, following acute tubular necrosis (ATN), and from a variety of drugs including aminoglycosides, cyclosporine, and cisplatin. Some cases of Bartter syndrome and all cases of Gitelman syndrome are hypomagnesemic [108 – 110]. Phosphate depletion is associated with magnesuria although the mechanism is not well understood. An additional category which should be considered is that of redistribution of magnesium within the body such as might occur after parathyroidectomy, i.e. hungry bone syndrome [20, 111] or in association with acute pancreatitis [112]. The renal losses are most commonly due to diuretic therapy and generally are mild because the volume contraction results in increased proximal reabsorption.

Clinical Consequences of Hypomagnesemia

Hypomagnesemia is often associated with other electrolyte abnormalities so that it may be difficult to ascribe the particular symptom to the low levels of magnesium. However, typical signs of magnesium deficiency are tetany and positive Chvostek and Trousseau signs as a manifestation of neuromuscular irritability [113]. Tetany may occur without frank hypocalcemia, but hypocalcemia is commonly present in severe magnesium deficiency. Abnormal cardiac function may be manifested by wide QRS with peaking of T waves and increased ventricular arrythmias. Hypokalemia is associated with hypomagnesemia in almost 50% of cases, possibly indicating that the causes for decreases in these electrolytes are similar. However, hypokalemia may be refractory to potassium supplementation until the magnesium deficit is corrected [114]. Severe hypocalcemia may coexist, and this is related to a profound defect in PTH secretion [115]. Magnesium replenishment results in a rapid increase in the release of PTH within minutes of administration [116]. The hypocalcemia of magnesium depletion is also due to a skeletal resistance to the actions of PTH [117].

Diagnosis and Therapy of Hypomagnesemia

Since measurement of magnesium is not routine, magnesium deficiency can often go unrecognized. Magnesium should be measured in the clinical circumstances mentioned above, and if low, should be replenished and the cause identified and corrected. Distinction between GI and renal losses can be made by measurement of 24-hour urine magnesium values or the fractional excretion of magnesium, since the normal renal response to magnesium deficiency is to increase magnesium reabsorption and to decrease magnesium excretion to low levels. Prophylactic administration of magnesium may be considered in certain clinical circumstances if renal function is normal. Potassium-sparing diuretics may be considered in cases of renal magnesium wasting. Replacement therapy should be by the oral route if possible, but parenteral administration can be utilized if the manifestations of hypomagnesemia are severe or if oral administration is not possible or limited because of the diarrhea induced by oral supplements.

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Primary Glomerulonephritis

Claudio Ponticelli and Giovanni B. Fogazzi

Approach to the Patient with Proteinuria and Microscopic Hematuria

Proteinuria and/or microscopic hematuria are typical findings in patients with glomerulonephritis (GN). However, they can also be associated with other renal or extrarenal disorders. Therefore, a stepwise approach is advisable for a proper evaluation (Figures 1 and 2).

When proteinuria (or more appropriately albuminuria) is detected by dipstick, a false positive should first be ruled out. This can be caused by urinary density > 1.025, urinary pH

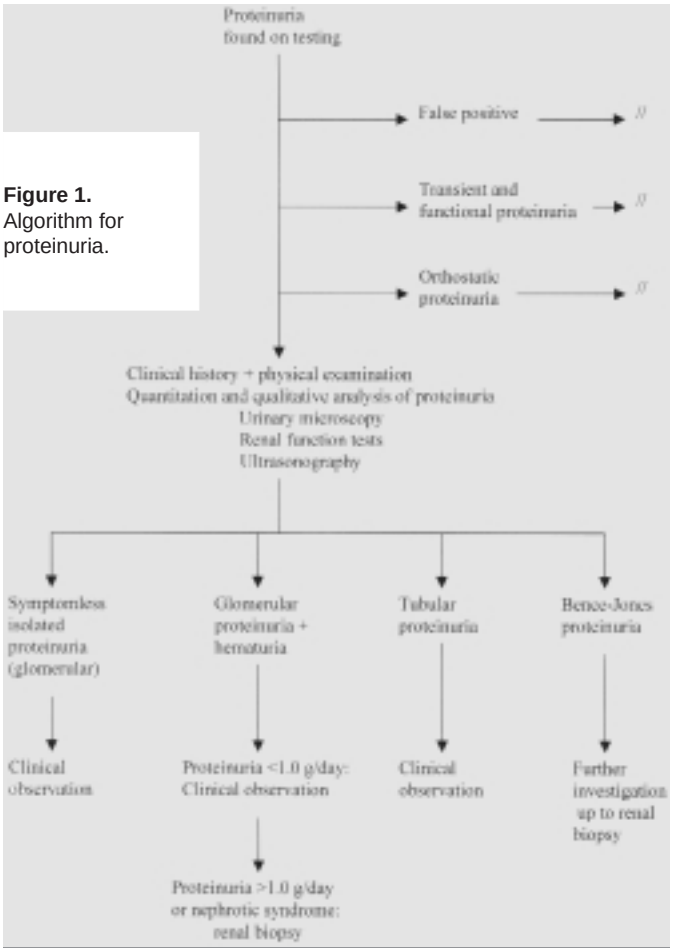

Figure 1. Algorithm for proteinuria.

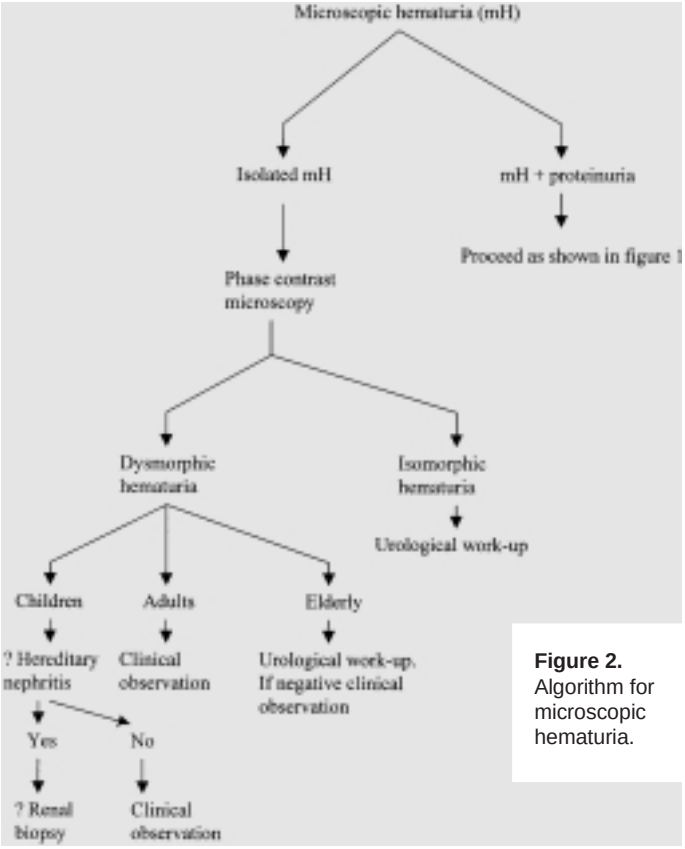

Figure 2. Algorithm for microscopic hematuria.

> 8.0, contamination of urine by quaternary ammonium compounds or phenazopyridine used for disinfection of urine containers, or by immersion of the dipstick in the urine for too long a period of time. It is also important to exclude clinical conditions that can cause transient and functional albuminuria, such as vigorous physical exercise, fever, or acute congestive heart failure (CHF) (Table 1). Especially in adolescents and young males, proteinuria may be purely orthostatic. This condition is characterized by the presence of proteins in urine collected on a standing position and complete absence in urine collected during recumbency. Even when orthostatic proteinuria is quantitatively important, the long-term prognosis is favorable, and no further investigation is needed. Clearly, orthostatic proteinuria differs from the quantitative increase of proteinuria that can be found in most patients with GN while they are standing [194].

If persistent nonorthostatic proteinuria is found, a complete work-up is necessary. This includes clinical history and physical examination, evaluation of renal function, the quantitation of proteinuria in g/24 hours or as albumin/creatinine ratio, the qualitative analysis of proteinuria by electrophoresis on cellulose acetate or agarose, or by sodium dodecyl sulfate-polyacryl-amide gel electrophoresis (SDS-PAGE) or other techniques, other appropriate laboratory tests, and ultrasonography of the kidneys and urinary tract.

In case of glomerular proteinuria, which is by far the most frequent condition seen in clinical practice, the clinical history may be

Table 1. Classification of Proteinuria and Main Clinical Associations

Transient/functional proteinuria
Strenuous physical activity
Fever
Acute congestive heart failure
Orthostatic proteinuria
Glomerular proteinuria
Primary and secondary glomerulonephritis
Isolated symptomless proteinuria
Proteinuria in morbid obesity
Tubular proteinuria
Acute and chronic tubulointerstitial diseases
Toxins and drugs
Primary and secondary glomerulonephritis
Overflow proteinuria
Monoclonal gammopathies (immunoglobulin light chains
Intravascular hemolysis (hemoglobin)
Rhabdomyolysis (myoglobin)
Leukemia (lysozyme)
Tissue proteinuria
Acute inflammation of urinary tract
Neoplasia of urinary tract

characterized by hereditary renal diseases, by a family predisposition to renal or systemic diseases such diabetes mellitus (DM) or systemic lupus erythematosus (SLE), or by allergy. In other cases, there may be a history of exposure to hydrocarbons or solvents, the use of potentially nephritogenic drugs, or a preceding infection. Physical examination may be normal or reveal arterial hypertension, morbid obesity (possibly associated with focal segmental glomerulosclerosis (FSGS) [152]), generalized or local edema with weight gain, weight loss, skin or joint changes, enlarged liver and spleen, macroglossia, lung disease, vascular disease, neurologic abnormalities or other findings. Basic laboratory tests include serum creatinine and/or glomerular filtration rate (GFR), glycemia, total serum proteins and protein electrophoresis, serum cholesterol, hemogram, plasma immunoglobulins, C3 and C4 levels, the search for HBs antigen and of hepatitis C antibodies, and tests for syphilis. More targeted tests are the search for neoplastic markers, antistreptolysin titer (ASO), cryoglobulins, antinuclear (ANA) and/or anti-DNA antibodies, rheumatoid factor (RF), antineutrophilic cytoplasmic antibodies (ANCA), or antiglomerular basement membrane (anti-GBM) antibodies. Ultrasonography may reveal normal or enlarged kidneys or reduction of size with increased hyperechogenicity or scarring.

If glomerular proteinuria does not exceed 1.0 g/24 hours and is associated with normal renal function and there is no hematuria, negative clinical history, negative physical examination, and normal ultrasonography, a diagnosis of symptomless isolated proteinuria can be made. In this case, no immediate further investigation is necessary, although long-term follow-up is indicated. For patients with proteinuria and microscopic hematuria, monitoring over time may be sufficient if proteinuria is < 1.0 g/day, but renal biopsy may be indicated for prognostic or genetic reasons. With proteinuria > 1.0 g/24 hours, renal biopsy is advisable. If proteinuria is in the nephrotic range (i.e. > 3.5 g/24 hours), with or without hematuria, renal biopsy is indicated unless there are unacceptable risks of complications. A frequent exception is represented by children with a selective proteinuria, which is usually caused by minimal change nephropathy responsive to glucocorticoids.

Tubular proteinuria usually does not exceed 1.5 – 2.0 g/24 hours. It may be caused by acute or chronic tubular disorders such as interstitial nephritis or heavy metal nephropathy. Tubular proteinuria is also present in GN with associated tubulointerstitial changes [9]. A pure tubular proteinuria needs to have the

Table 2. The Main Causes of Microscopic Hematuria (modified from [57])

Renal parenchymal disease	*Urinary tract disease*
Primary and secondary glomerulonephritis	Trauma/surgery
Glomerular C3 deposition	Neoplasia
Alport's syndrome	Angioma
Thin glomerular basement membrane disease	Obstructive uropathy
Interstitial nephritis	Cysts
Analgesic nephropathy	Varices/teleangiectasia
Pyelonephritis	Papillary necrosis
Sickle cell disease	Periureteritis
Polycystic kidney	Ureterocele
Loin pain hematuria syndrome	Endometriosis
Trauma/surgery	Infections
Renal biopsy	Infestations
Jogger's nephritis	Radiation
	Diverticulum
Renal vessel disease	Cyclophosphamide-induced cystitis
C3 arteriolar deposition	Ex vacuo hematuria
Arteriolar emboli or thrombosis	Prostatitis
Renal vein thrombosis	Prostatic hypertrophy
Arterial or venous malformations	Urethritis
Arteriovenous fistula (idiopathic, cirsoid, acquired)	Urethral prolapse
Nutcraker's syndrome	Urethral caruncle
	Meatal ulcers
	Condyloma acuminatum
	Foreign bodies
	Catheters
	Long-distance running
	Systemic coagulation disorders
	Platelet defect
	Coagulation protein deficiency
	Scurvy
	Anticoagulant treatment

cause identified. In these cases, clinical history is of particular importance. Tests exploring the function of proximal tubules are necessary. No renal biopsy is usually needed. Observation over time is advisable.

Among the various types of overflow proteinuria, the most clinically relevant is represented by the increased excretion of monoclonal immunoglobulin light chains, better known as Bence-Jones proteinuria. This is caused by monoclonal gammopathies such as multiple myeloma, AL amyloidosis, light chain deposition disease, or some types of cryoglobulinemia. It is worth remembering that dipsticks do not react with immunoglobulin light chains, leading to false negative results. In some of these disorders a glomerular proteinuria can also be found because of the damage caused by the deposition of light chains in the glomeruli. Immunofixation is the best method to characterize the monoclonal component. Further clues to the diagnosis are the search for a monoclonal peak in the blood, quantitation of plasma immuno-

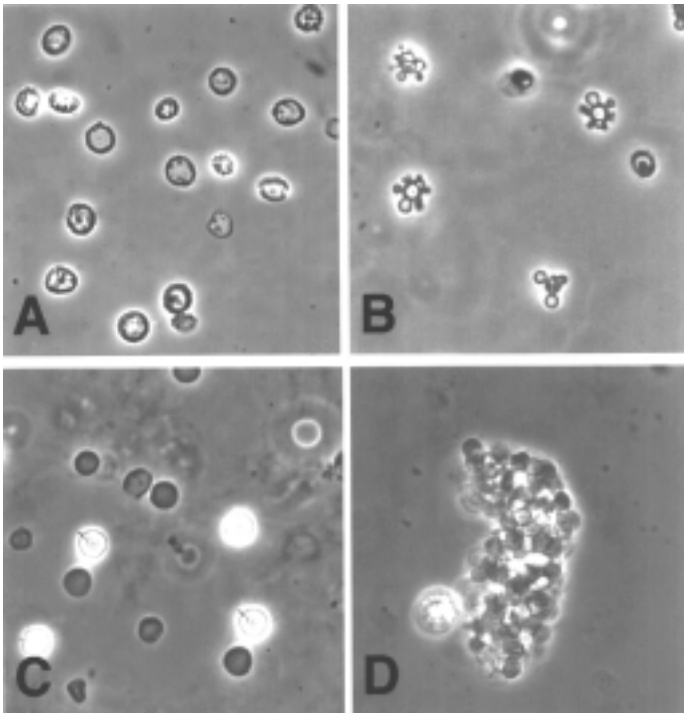

Figure 3. A: dysmorphic urinary erythrocytes. B: acanthocytes. C: isomorphic erythrocytes. D: erythrocyte cast. (Phase contrast microscopy, 400x).

globulins, bone marrow aspiration or biopsy, bone X-rays, abdominal fat pad or rectal biopsy, and renal biopsy.

Microscopic hematuria indicates the presence in the urine of an abnormal amount of erythrocytes, which can be the consequence of a large number of disorders (Table 2). When microscopic hematuria is associated with proteinuria, a diagnosis of GN is likely. The cause of symptomless, isolated, microscopic hematuria can be much less clear. This is usually found by chance by dipsticks, which have a 91 – 100% sensitivity and a 65 – 99% specificity [198]. False negative results can occur with high concentrations of urinary ascorbic acid [22], while false positives are caused by myoglobinuria or bacteriuria [107]. Microscopy is necessary, not only to confirm a positive dipstick, but also to separate a glomerular from a nonglomerular bleeding on the basis of erythrocyte morphology. In fact, when hematuria is caused by a glomerular disease, "dysmorphic" erythrocytes and acanthocytes predominate in the urine (Figures 3A and 3B), while normal or "isomorphic" erythrocytes (Figure 3C) predominate in nonglomerular bleeding [45, 100]. The presence of erythrocyte/hemoglobin casts (Figure 3D) is pathognomonic of bleeding of the renal parenchyma. However, the sensitivity is low, approximately 20 – 30%. Phase contrast microscopy is by far superior to conventional bright field microscopy in revealing these findings.

We consider the analysis of the urinary sediment as a key step in the work-up of patients with isolated microscopic hematuria [57]. When dysmorphic hematuria is found on repeated examination, a diagnosis of chronic glomerular disease is likely. All glomerular diseases can cause symptomless isolated microscopic hematuria, but immunoglobulin A (IgA) nephropathy, non-IgA mesangial or focal proliferative glomerulonephritis (FPGN),

and thin basement membrane disease are the most frequently found when renal biopsy is performed [77, 185]. The work-up of these patients differs according to their age. In children and adolescents, hereditary nephritis such as Alport's syndrome or thin basement membrane disease has to be suspected first. An accurate family history should be taken and family members investigated for microscopic hematuria, renal function impairment, deafness, and/or ocular abnormalities. A renal biopsy should be performed in case there is a suspicion of Alport's syndrome. However, when the family findings suggest benign hematuria the indication for renal biopsy is less definite. If the family history and investigation are negative for hereditary nephritis, renal biopsy is not strictly necessary, and clinical observation may be sufficient. However, ultrasonography of the kidneys and of the urinary tract is always necessary to exclude urological disorders.

In young and middle-aged adults, dysmorphic microscopic hematuria is more likely caused by primary glomerulonephritis such as IgA nephropathy or other less defined glomerular diseases, although thin basement membrane is still a possibility. The measurement of serum immunoglobulins may show increased IgA levels, which are found in 30 – 50% of patients with IgA nephropathy. A persistent decrease of C3 serum level may indicate a type II membranoproliferative glomerulonephritis (MPGN) or, especially in young women, SLE. Rarely, microscopic hematuria may be the only sign of anti-GBM disease, of systemic vasculitis, or of other systemic diseases. Clinical observation is needed, and renal biopsy should be considered in case of appearance of proteinuria, renal function impairment, or definite signs of a systemic disorder. For these patients, ultrasonography of the kidneys and the urinary tract is mandatory in the initial work-up to exclude other causes of microscopic hematuria such as stones, polycystic kidney, and tumors.

In the elderly, especially in males, microscopic hematuria is frequently the first and only sign of tumor of the urinary tract. Thus, even in the presence of a dysmorphic hematuria, a full urological work-up is recommended. If no urological abnormalities are found, an underlying GN is possible, as in the previous categories [185]. Clinical observation is sufficient, although a tumor of the urinary tract can be associated with a glomerular disease.

The prognosis of patients with symptomless isolated microscopic hematuria of renal origin is usually good, as demonstrated by several studies both in children and adults [77, 133, 170]. In fact, most patients continue to have microscopic hematuria, although it completely disappears in other patients. A minority of patients develop hypertension with or without proteinuria, but renal function impairment usually does not occur.

Pathogenesis, Complications, and Treatment of the Nephrotic Syndrome

The term nephrotic syndrome refers to a clinical condition characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The nephrotic syndrome is often seen with urinary protein excretion > 3.5 g/24 hours and is almost invariably present when proteinuria is > 5 g/24 hours. The nephrotic condition may expose the patient to disabling and even life-threatening complica-

Table 3. Main Complications of the Nephrotic Syndrome

Complication	*Pathogenesis*	*Treatment*
Proteinuria	Alterations in glomerular barrier	Moderate protein restriction ACE inhibitors AT1 receptor antagonists, NSAID
Hypoalbuminemia	Urinary loss Increased catabolism Insufficient liver synthesis	Reduction of proteinuria
Lipid abnormalities (Increased LDL, VLDL, lipoprotein(a))	Increased synthesis Reduced catabolism	CoA reductase inhibitors
Edema	Hypoalbuminemia (underfill mechanism) Resistance to ANP (overfill mechanism)	Thiazide agents Loop diuretics
Hypercoagulability	Increase in prothrombotic factors Decrease of anticoagulant proteins	Oral anticoagulation (?)

tions such as infections, bone disease, intravascular thrombosis, and cardiovascular disease (Table 3). Moreover, the onset of the nephrotic syndrome is a marker for bad prognosis for most glomerular diseases.

Proteinuria

Proteinuria is a consequence of the disruption of the permeselectivity caused by the disease-related functional and/or anatomical damage of the glomerular basement membrane (GBM). Plasma proteins, particularly albumin, are allowed to pass through the glomerular capillary wall, exceeding the tubular reabsorptive capacity. There is now evidence that proteinuria may play a role in the progression of chronic renal failure (CRF). The abnormal filtration of proteins brings them into contact with the mesangium and with the proximal tubular cells. Mesangial accumulation of proteins may produce mesangial cell injury, mesangial cell proliferation, and increased production of mesangial matrix that eventually lead to glomerulosclerosis [158]. The proximal reabsorption of proteins may trigger upregulation of inflammatory and vasoactive genes such as MCP-I and endothelins. The corresponding molecules formed in an excessive amount by renal tubuli are secreted toward the basolateral compartment of the cell and give rise to an inflammatory reaction that leads to renal scarring [158].

Eradication of the underlying glomerular disease represents the best treatment for proteinuria. Some reduction of urinary protein excretion may also be obtained with diet and/or drugs. While a high-protein diet increases proteinuria, a low-protein diet may reduce urinary albumin excretion and increase serum albumin levels, at least in the short-term [93]. ACE inhibitors can have an

antiproteinuric effect, which is dose-dependent. The effect may require some weeks to be complete and is blunted by sodium intake [74]. Angiotensin II (ANG II) receptor AT1 antagonists have a comparable antiproteinuric effect [61]. ACE inhibitors may also slow the progression of chronic renal insufficiency. This beneficial effect may be independent of the blood pressure reduction and is particularly marked in patients with proteinuric glomerular diseases [117]. Diet protein restriction, around 0.8 g per kg/day plus urinary losses, in combination with ACE inhibitors at the highest tolerated doses and restricted sodium intake may be recommended in patients with glomerular diseases to reduce urinary protein excretion and preserve renal function. It is possible but still unproven that the addition of AT1 receptor antagonist may further potentiate the antiproteinuric effect.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce proteinuria by ≥ 50% or more. The effect is rapid (within 1 week) and reverses after cessation of treatment. Indomethacin (150 mg/day) and meclofenamate (200 – 300 mg/day) are the 2 agents used most frequently. These agents can cause hyperkalemia, sodium retention, and acute renal failure (ARF) triggered by vasoconstriction or interstitial nephritis. Thus, careful monitoring of renal function is mandatory during treatment of nephrotic patients. The association with ACE inhibitors potentiates the antiproteinuric effect but increases the risk of renal function deterioration and hyperkalemia.

Hypoalbuminemia

Hypoalbuminemia plays a pivotal role in many complications of the nephrotic syndrome, including edema, malnutrition, hyperlipidemia, and cardiovascular disease. The urinary loss of albumin is not sufficient to explain hypoalbuminemia. There is also an increased catabolism of albumin that might contribute to hypoalbuminemia. However, the most important mechanism is the inability of the liver to increase the albumin synthesis in response to urinary losses and/or increased catabolism [93].

Neither albumin infusion nor a high-protein diet may increase serum levels of albumin because these measures result in increased urinary losses of albumin.

Lipid Abnormalities

In nephrotic patients, there is an increase in low density lipoproteins (LDL), very low density lipoproteins (VLDL), and lipoprotein (a) (Lp(a)) levels while high density lipoprotein (HDL) levels are either normal or decreased. The composition of lipoproteins is also altered with a relative increase in cholesterol. These abnormalities are caused both by an increased hepatic synthesis and by a decreased clearance of lipids and lipoproteins. Experimental and clinical studies showed that cholesterol synthesis increased in response to hypoalbuminemia, serum cholesterol being inversely proportional to serum albumin. In addition to the increased synthesis, there are alterations in catabolism of lipids in nephrotic syndrome caused mainly by a decreased activity of the enzyme lipoprotein lipase. This may be related either to the urinary loss of some activators of the enzyme or to an increase in free fatty acids that are known to inhibit lipoprotein lipase activity. The reduction of HDL levels may be attributed to the urinary loss of lecithin-cholesterol acyltransferase and/or to its inhibition caused by the increased levels of free lysolecithin produced in hypoalbuminemia [73]. There has been controversy in the past about the possible role

of hyperlipidemia in favoring cardiovascular complications. More recently an association between lipid abnormalities and coronary artery disease has been demonstrated in nephrotic patients [138].

A lipid-lowering diet (< 200 mg/day of cholesterol, total fat < 30% of total calories, and polyunsaturated fatty acids about 10% of total calories) is usually recommended as the first therapeutic step in patients with hypercholesterolemia. However, for many nephrotic patients, diet is not sufficient to correct hyperlipidemia. Various lipid-lowering drugs such as probucol, nicotinic acid, resins, and fibric acid derivates have been used with little success because these agents are either poorly tolerated or have little efficacy. At present, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are considered the drugs of choice for treating the hyperlipidemia of nephrotic patients. These agents may decrease serum cholesterol 30 – 40%, LDL about 40%, and apolipoprotein B 30%, but do not reduce the elevated levels of the atherogenic LP(a). The tolerance is usually good. Mild and transient increase in serum transaminase is rarely seen. Myositis and myalgias are rare but can occur with large doses.

Edema

Edema is one of the cardinal features of the nephrotic syndrome. Its pathogenesis is incompletely understood. Two main theories have been proposed: the classical underfill theory and the overfill theory. According to the classical view, hypoalbuminemia represents the "primum movens" of edema. Decreased plasma oncotic pressure favors translocation of fluid from the intravascular space into interstitial space. Reduction of plasma volume activates the renin-angiotensin system, secondary salt and water retention, plasma dilution, and further aggravation of hypoalbuminemia. However, only a minority of nephrotic patients have a decreased intravascular volume. The majority show normal or expanded plasma volume. Moreover, the plasma levels of renin, angiotensin, and aldosterone show large variations in nephrotic patients. Finally, maneuvers that increase plasma volume do not always result in a natriuretic response [139]. The overfill theory attributes a key role to the inability of the diseased kidney to excrete salt and water, with consequent intravascular expansion, increase in capillary hydrostatic pressure, and transudation of fluid into the interstitial space. The enhanced tubular NaCl avidity is mainly caused by post-receptor resistance to the action of atrial natriuretic peptide, due to enhanced activity of cyclic GMP phosphodiesterase [80]. Although the overfill theory may account for most cases of nephrotic edema, it is possible that underfill mechanisms are involved in few other cases, especially during the edema acquisition phase.

In milder cases, edema may be handled by restricting dietary sodium intake. Diuretic therapy may be required in patients who do not respond to a low-sodium diet. The first step may consist of administration of hydrochlorothiazide (12.5 – 50 mg/day), preferably in combination with a potassium-sparing agent such as amiloride, triamterene, or spironolactone. Loop diuretics, such as furosemide, ethacrynic acid, or bumetanide are needed for more severe edema. Furosemide is the most-used agent because of its flexibility and good tolerance. The drug may be given by mouth or intravenously, at doses ranging between 25 and 2000 mg/day. Binding of the drug to tubular fluid albumin can blunt the diuretic response. In patients who do not respond to high-dose furosemide, combining it with diuretics acting at different

levels, such as hydrochlorothiazide (25 – 50 mg/day) or metolazone (2.5 – 10 mg/day), may maximize the diuretic response.

Coagulation Abnormalities

In the nephrotic syndrome, there is an imbalance between procoagulant/antithrombotic factors. Usually there is an increase of prothrombotic factors such as fibrinogen, factors V and VIII, factor VII, platelets, and platelet hyperaggregability. Anticoagulant proteins such as active protein S, active protein C, antithrombin III are decreased, due to loss in the urine. In addition, nephrotic patients may show hyperviscosity favored by hyperlipidemia and impaired fibrinolysis, caused by elevated Lp(a) and ANG IV levels that promote the synthesis of plasminogen activation inhibitor. These hemostatic abnormalities promote the synthesis of plasminogen activation inhibitor and determine a hypercoagulable state that may cause thromboembolic complications. Renal vein thrombosis, deep vein thrombosis and pulmonary embolism are the most frequent thrombotic complications of the nephrotic syndrome and are roughly correlated with the magnitude of the depression of serum albumin. Their incidence is lower in children than in adults, but children are more exposed to the risk of arterial thrombosis.

Anticoagulant drugs can reduce the risk of thrombosis. However, because they carry a substantial risk of hemorrhagic complications, their use is generally restricted to situations such as prolonged bed rest, surgery, and episodes of dehydration. On the other hand, decision analysis studies reported that the benefits of prophylactic anticoagulants outweigh the risks, at least in nephrotic patients with membranous nephropathy who are particularly exposed to the risk of intravascular thrombosis [162].

Infections

Nephrotic patients have an increased susceptibility to infections. Several factors may be responsible: urinary loss of immunoglobulins, urinary loss of complement factors B and D, defective cellular immunity caused by the urinary loss of zinc, transferrin and vitamin D, and malnutrition. The concomitant use of high-dose glucocorticoids and immunosuppressive agents may further increase the risk of infections.

Endocrine Abnormalities

Nephrotic patients have significant urinary losses and reduced plasma concentration of $25(OH)D_3$. However, the vitamin D binding protein is also reduced in the nephrotic syndrome, so that the free $1,25(OH)_2D_3$ remains at normal plasma levels. Hypocalcemia is frequently seen in nephrotic patients. In most cases, it may be attributed solely to the reduction in protein-bound calcium secondary to hypoalbuminemia. Thus, while many nephrotic patients may show decreased serum levels of $25(OH)D_3$ and calcium, the serum-free $1,25(OH)_2D_3$ and ionized calcium are normal so that treatment with vitamin D is not necessary. However, vitamin D supplements are indicated in a minority of patients who demonstrate evidence of reduced serum ionized calcium, reduced intestinal calcium absorption, and secondary hyperparathyroidism.

Urinary losses of thyroxin-binding globulin can occur in the nephrotic syndrome. However, the serum levels of T4 and thyrotropin are normal, and clinically most patients are euthyroid.

Table 4. Factors Associated with Minimal Change Nephropathy

Drugs	*Tumors*
Nonsteroidal anti-inflammatory drugs	Hodgkin's lymphoma
Lithium	Non-Hodgkin's lymphoma
Thiola	Leukemia
Gold	Mesothelioma
Trimethadione-paramethadione	Carcinoma of colon, prostate, pancreas, or lung
Mercury	Nephroblastoma
Penicillamine	Waldenstrom's
Ampicillin	
Interferon	
Other diseases	
Diabetes mellitus	*Allergy*
Dermatitis herpetiformis	Pollens
Schistosomiasis	Food allergy
Virus infections	House dust
Immunizations	Bee stings

Minimal Change Disease (MCD)

MCD, also called minimal change nephropathy, nil disease or, lipoid nephrosis, is the most common cause of the nephrotic syndrome in children but may also occur in adults and the elderly. Clinically, MCD is characterized by a pure nephrotic syndrome. There are few or no abnormalities on light microscopy and immunofluorescence. The typical lesion is represented by a diffuse effacement of the foot processes of the podocytes on electron microscopy. The disease usually responds to glucocorticoids. In many patients the course is punctuated by alternating remissions and relapses of the nephrotic syndrome. Although there is evidence that MCD and FSGS may represent the 2 extremes of the same disease, we will treat these entities separately as they have a different histologic picture, clinical presentation and outcome, and response to therapy.

Etiology and Epidemiology

MCD may affect siblings in 3.5% of cases. An indication for a possible genetic predisposition is the reported association with certain HLA antigens such as B12, B8, and Drw 7. However, not all studies confirm this association [169]. Atopic diseases such as asthma, eczema, and hay fever may be present in almost one-third of patients with MCD. In a number of patients MCD may develop after allergic episodes.

Although MCD is usually idiopathic, rare cases occurring in association with drugs or other diseases have been reported (Table 4). MCD and acute interstitial nephritis may develop after the use of NSAIDs. Most of the affected patients are elderly and develop a nephrotic syndrome with ARF while taking the drug. Renal signs usually improve after discontinuing the drug with or without glucocorticoids [161]. Lithium and thiola, a drug used for treating cystinuria, may also cause MCD. Some cases of nephrotic syndrome and MCD have been observed during administra-

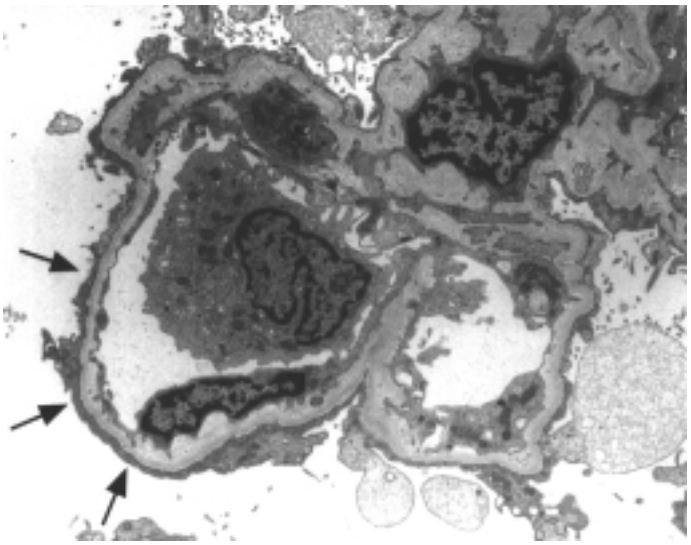

Figure 4. Minimal change nephropathy. Severe effacement of foot processes (arrows)(electron microscopy, 7,500x).

tion of interferon [44]. Usually nephrotic syndrome reverses after discontinuation of the drug. MCD may also be associated with DM, schistosomiasis, and other diseases, including neoplasias. The most frequent association with malignancy is with Hodgkin's lymphoma, while the association with non-Hodgkin's lymphoma or solid tumors is rare.

Pathology

On light microscopy, glomeruli may be completely normal with normal capillary walls and cellularity. However, a mild and focal mesangial hypercellularity may be noted. On morphometric analysis, glomerular hypertrophy may be seen in some cases. This finding may predict the progression to focal glomerulosclerosis [58]. Immunofluorescence is usually negative, but mesangial IgM deposition may be seen in some cases, with or without a slight increase in mesangial matrix. Some investigators have proposed that the presence of IgM deposits could identify a separate entity, but affected patients can neither be differentiated clinically from patients without IgM deposition nor have a different outcome and response to treatment. Also, the presence of mesangial IgG should be considered as nonspecific.

Electron microscopy shows the typical features of MCD consisting of an effacement of the foot processes of podocytes (Figure 4). The GBM is mostly normal; no parietal deposits are present. The endothelial cells are often swollen.

Pathogenesis

A number of studies have suggested that alterations in glomerular charge sites play an important role in MCD. A decreased glomerular negative charge has been found in rats with nephrotic syndrome caused by puromycin aminonucleoside [15]. Intrarenal arterial infusion of polycations causes selective proteinuria and foot processes effacement [8], and a decreased staining for glomerular polyanions has been observed in renal biopsies from patients with MCD [21]. The loss of

anionic charges on glomerular structures prevents the electrostatic repulsion between negatively-charged structures, which is a fundamental constituent of glomerular filtration barrier. As a consequence, there is retraction and effacement of foot processes, which are normally negatively charged, and there is a passage of lower macromolecules, such as serum albumin, into the urine. However, it is possible that the disturbance in charge is not confined to the glomerulus. Ghiggeri et al. showed that the charge and conformation of serum albumin were modified in the nephrotic phases of MCD but returned to near normal values after steroid-induced remission of proteinuria [62]. Levin et al. found an early reduction of surface negative charge on red blood cells (RBCs) and platelets preceding reduction of serum albumin during relapses [111]. Thus, MCD may result both from loss of negative glomerular charge (due to a loss of glomerular polyanions) and from a generalized electrochemical disorder with increased positive charge of some extrarenal structures, including serum albumin (Figure 5).

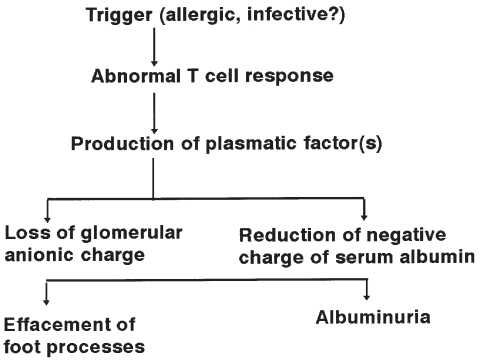

Figure 5. Possible pathogenesis of minimal change nephropathy.

What is the primary cause of these electrostatic defects? The abnormalities might be a consequence of failure to synthesize the charged group, loss of anionic charges due to degradative process, or neutralization. These mechanisms might arise from a circulating charge-neutralizing factor that could be produced by T cells in response to an infective or allergic trigger. A number of studies reported that during MCD relapses, lymphocytes have impaired responses to polyclonal activators, probably caused by prostaglandins secreted by macrophages. The response returns to normal during remission. On the other hand, there is an increase in T-suppressor activity during relapse that reverses after treatment. However, it is still unclear whether these and other abnormalities of the cell-mediated immunity are the cause or the consequence of the nephrotic syndrome and/or of circulating factor(s). Several lymphokines, including interleukin-2, and vascular permeability factors were isolated in the supernatant of cultured lymphocytes. These factors might be responsible of the loss of anionic charges and increased glomerular permeability, but their pathogenic role is still far from being established.

Clinical Presentation and Course

MCD is the major cause of the nephrotic syndrome in children, accounting for 90% of cases under the age of 6. The disease is not limited to children, however. It may occur in adulthood and also in the elderly.

Patients with MCD generally present with full-blown nephrotic syndrome. The onset of the disease is usually acute and frequently follows a viral upper respiratory infection, an allergic episode, or a vaccination. The degree of pedal and periorbital edema may be variable, but most patients have a severe fluid retention that can also result in ascites and pleural effusion. Blood pressure is usually in a normal range but is higher than in normal

Table 5. Definitions of Responses and Relapses in Patients with Minimal Change Nephropathy

Complete remission	Proteinuria < 4 mg/m^2/day in children or < 0.2 g/day in adults for 3 consecutive days
Partial remission	Proteinuria between 4 and 40 mg/m^2 day in children or between 0.21 and 3.5 g/day in adults for 3 consecutive days
Relapse of proteinuria	Proteinuria > 4 mg/m^2/day in children or > 0.2 g/day in adults for at least one week in patients who were in complete remission
Relapses of nephrotic syndrome	Proteinuria > 40 mg/m^2/day in children or > 3.5 g/day in adults for at least one week in patients who were in remission
Frequent relapsers	Patients with ≥ 2 episodes of the nephrotic syndrome in 6 months or ≥ 3 episodes of the nephrotic syndrome in 12 months
Steroid-dependent	Reappearance of the nephrotic syndrome within 2 weeks after reduction or discontinuation of glucocorticoids

subjects of the same age. About 20 – 30% of patients are hypertensive. On the other hand, hypovolemic shock may sometimes occur as a consequence of massive urinary loss of albumin. Proteinuria ranges between 3 and 20 g or more per day. It is typically selective with heavy loss of smaller macromolecules, such as albumin and transferrin, while proteins of higher molecular weight are retained. Severe hypoalbuminemia and hypercholesterolemia are common. Microscopic hematuria can be found in about one-third of cases. Renal function is usually normal. However, moderate to severe renal failure can occur, particularly in older patients.

It is difficult to assess the natural course of MCD because today most patients are treated with glucocorticoids and other effective drugs. Before the use of these agents, the 5-year mortality rate in children was as high as 67%, with the remaining patients undergoing spontaneous remission [6]. The major causes of death were infection, particularly peritonitis and pneumonia, and renal failure. A beneficial alteration in the course of MCD was achieved with glucocorticoids (see below). Approximately 95% of children and 80% of adults can obtain complete remission of proteinuria under glucocorticoid therapy. In those who respond, the remission is permanent in only about 20 – 25%. Another 20 – 25% of patients will have infrequent relapses, while the rest become frequent relapsers or steroid-dependent (see Table 5). The risk of relapse seems to be inversely correlated with age, being higher in children younger than 6 years than in older children [186]. The risk is lower in adults [60] and even lower in the elderly [113]. The risk of frequent relapses and/or steroid dependency is lower in patients who had a good response to glucocorticoids, a prolonged initial treatment [24], and a prolonged remission after the first episode [112]. As already mentioned, the presence of glomerular hypertrophy on morphometric analysis is a bad prognostic sign, because it may herald progression to FSGS [58]. Although in the past mesangial hypercellularity

and mesangial IgM deposits were thought to be associated with a decreased response to glucocorticoids and steroid dependency, the current opinion is that these findings are not associated with outcome or response to treatment different from those of patients with classic MCD. Eventually, about 65 – 75% of patients may enter a prolonged remission within 10 years from clinical onset, but some children need 20 – 30 years before attaining a definitive remission.

Progression to CRF is exceptional in children but may occur in adults and particularly in elderly patients. Sporadic cases of ARF have also been reported. These can be due to hypovolemia, renal vein thrombosis, or interstitial nephritis, but are more often caused by diuretics or hemodynamic factors [177]. ARF is more frequent and severe in elderly patients but can also rarely occur in children. MCD patients are exposed to the complications of the nephrotic syndrome, such as infections and intravascular thrombosis, or its treatment. Some patients may die as a result of these complications. The mortality rate ranges around 2% for children [112], 65 – 10% for adults [167], and 35 – 45% for elderly patients [113]. Death is particularly frequent in patients with renal dysfunction and in those untreated or refractory to treatment [135].

Diagnosis

MCD may occur in the first year of life but this is rare. In these cases, it is difficult to distinguish MCD from the Finnish type of congenital nephrotic syndrome and diffuse mesangial sclerosis. Congenital nephrotic syndrome is more common in Finland but has also been observed in other countries. It is an inherited autosomal recessive disease characterized by a severe nephrotic syndrome from the first days of life. There are no definite histopathologic criteria that allow differentiation between it and MCD. Diffuse mesangial sclerosis is another entity which also has an early onset and a severe nephrotic syndrome but differs in its rapid progression to end-stage renal failure and by histopathologic lesions characterized by a combination of thickened basement membranes and expansion of mesangial matrix with no increase in the number of mesangial cells [25].

It is difficult to differentiate MCD from other glomerular diseases on clinical grounds. Selective proteinuria is more frequent in MCD but can also be found in the initial stages of membranous nephropathy and FSGS. Hypertension, hematuria, and renal insufficiency are more common in other glomerular diseases, but there is considerable overlap. Because MCD is responsible for most cases of nephrotic syndrome in children, treatment with glucocorticoids is usually initiated on empirical grounds, and renal biopsy is performed only if an 8-week trial does not induce remission of proteinuria. In adults MCD is a rarer cause of the nephrotic syndrome. A trial with glucocorticoids is not helpful for an early diagnosis, as only 50 – 60% of adults show disappearance of proteinuria after 8 weeks of prednisone. Thus, renal biopsy is required in adults.

Treatment

MCD is very sensitive to treatment with glucocorticoids. Although remission may occasionally be obtained with relatively moderate doses, most authorities suggest an aggressive initial treatment. In children the standard treatment for the first episode of nephrotic syndrome consists of prednisone at a dose of 60 mg/m^2/day for 4 weeks, followed by 40 mg/m^2 given on alternate days for 4 more weeks [24]. With such a regimen, proteinuria

can be expected to disappear in about 50% of children within one week, in 80 – 85% within 4 weeks, and in 90 – 95% within 8 weeks. In a few children, however, complete remission of proteinuria occurs only after more prolonged treatment or after intravenous (IV) high-dose methylprednisolone [25].

Adults are usually treated with lower doses of prednisone, i.e. 1 mg/kg body weight/day. Proteinuria disappears only in 50 – 60% of adults within 8 weeks. However, about 80% of patients become free of proteinuria if treatment is prolonged to ≥ 16 weeks [60, 134]. Thus, it is now clear that the concept of steroid resistance, which was previously applied to patients who did not respond to high-dose prednisolone within 4 – 8 weeks, should be reviewed. Many adults and some children who were considered as steroid resistant in the past were simply undertreated.

There is, however, a small proportion of patients with the histological appearance of MCD who do not respond even to a prolonged treatment with steroids. These patients usually show FSGS on repeated biopsy and should be treated accordingly.

After remission is obtained, some 20 – 30% of patients do not relapse, and a similar number have only infrequent relapses. Patients with infrequent relapses are usually treated with high-dose prednisone until remission, followed by 4 weeks of alternate-day prednisone at a dose of 40 mg/m^2 in children and 0.75 mg/kg in adults [147]. Spontaneous remission is also possible, particularly when relapse follows an intercurrent infection.

Unfortunately, many initial responders either become frequent relapsers or show steroid dependency. There is some evidence that the risk of relapse is greater in children given a short course of treatment for the initial attack than in children given long-term treatment [24]. Thus, after remission has been obtained, it is advisable to prolong treatment to prevent further relapses. If well tolerated, low-dose prednisone can be given every other day for 6 – 12 months. The doses of steroid should be tapered gradually to prevent relapses that may be triggered by secondary hypoadrenalism.

The treatment of frequently relapsing or steroid-dependent patients is difficult. For inducing remission, schedules based on alternate-day prednisone, low-dose hydrocortisone, and IV high-dose methylprednisolone followed by low-dose prednisone can reduce iatrogenic toxicity. However, in spite of these schedules, a number of patients develop steroid-related side effects, including obesity, diabetes, osteoporosis, Cushingoid features, hypertension, infection, and growth retardation in children.

Levamisole, cytotoxic agents, and cyclosporin have been suggested as potential alternative treatments. Levamisole is an antihelminthic drug with immunomodulating properties. Some retrospective studies reported that this agent could reduce the risk of relapses. Conflicting results have been obtained with controlled trials. In one study [23], 61 steroid-dependent children, in whom remission had been achieved with prednisone, were randomly assigned to receive placebo or levamisole at a dose of 2.5 mg/kg every other day. After 112 days, 4 of 30 patients given placebo vs. 14 of 31 given levamisole maintained remission, the difference being significant. However, another controlled trial could not find any significant difference in the median duration of remission between children given placebo and those given levamisole [41].

Cytotoxic agents, such as cyclophosphamide and chlorambucil, can produce more lasting remission than steroids. Remission seems to be more stable in adults than in children. More than 60% of adults given cyclophosphamide because of multiple relapses remained in remission for at least 5 years [115,

134], while a pediatric review reported that the rates of remission at 5 years in children ranged from 36 – 66% [25]. Duration of treatment is also important. Pennisi et al. reported complete remission at one year in 92% of children given cyclophosphamide for 10 – 12 weeks vs. 42% of children treated for 6 – 8 weeks [141].

Alkylating agents may cause leukopenia, hemorrhagic cystitis, oncogenic effects, and gonadal toxicity, testes being more vulnerable than ovaries. Therefore, their use should be limited to those patients who are at risk of developing steroid toxicity. To prevent leukopenia, high daily doses should not be used (we suggest 2 mg/kg/day for cyclophosphamide and 0.1 – 0.15 mg/kg/day for chlorambucil). To prevent azoospermia, cumulative doses of 200 – 250 mg/kg for cyclophosphamide or 10 – 15 mg/kg/day for chlorambucil should not be exceeded. With these cumulative doses, the oncogenic risk is minimal. Forced diuresis and/or 2-mercaptoethanesulphonate (MESNA) can protect from the bladder toxicity of cyclophosphamide.

Cyclosporin is another therapeutic option. Most steroid-dependent patients can be maintained in remission with cyclosporin, which is usually started after remission has been induced with steroids [145]. After cyclosporin is stopped, an early relapse of nephrotic syndrome usually occurs, but some patients may maintain remission, particularly if cyclosporin dosing has been tapered gradually after prolonged treatment. A number of side effects may be associated with the use of cyclosporin. Hypertrichosis, gum hyperplasia, gastrointestinal symptoms, and hypertension are the most frequently reported. There has been much concern about the potential nephrotoxicity of cyclosporin. In patients with nonrenal autoimmune diseases, a cyclosporin-related nephropathy characterized by interstitial fibrosis and progressive renal disease can develop. This is usually preceded by a typical arteriolopathy with either nodular proteinaceous deposits in the arteriolar wall or mucinoid thickening of the intima. Older age, high doses of cyclosporin, and an increase in plasma creatinine to > 75% over the basal values are the most important variables associated with the risk of developing irreversible cyclosporin nephropathy [55]. The importance of the size of the dose in inducing nephropathy is confirmed by some studies based on iterative renal biopsies in patients with MCD [70, 123]. On the other hand, there is evidence that cyclosporin arteriolopathy, which precedes the development of interstitial fibrosis, can be reversible if cyclosporin is stopped or given at lower doses [129]. Thus, cyclosporin can be used in patients with resistant disease, but careful monitoring is needed with its use in patients with renal diseases. We suggest as an initial dose 4 mg/kg/day of the new microemulsion in adults and 100 mg/m^2/day in children. Trough blood levels should be maintained between 75 and 200 ng/mL. The doses should be reduced if plasma creatinine rises > 30% over the basal values. The drug should be stopped if plasma creatinine rises > 75% over the basal values.

In summary, we suggest the following approach in MCD. An aggressive and prolonged (if tolerated) course of glucocorticoids should be used to treat the first episode of nephrotic syndrome in an attempt to achieve remission and prevent relapse. Infrequent relapses can be treated with shorter courses of glucocorticoids. In frequently relapsing/steroid-dependent patients, levamisole may be tried in an attempt to reduce steroid doses in responders. Although the efficacy of this drug is controversial, the tolerance is usually good. If levamisole is not successful, patients may be treated with continuous alternate-day prednisone and IV methylprednisolone pulses dur-

ing relapses. Those patients who do not tolerate steroids may be given a trial with a cytotoxic agent for 12 weeks at cumulative doses not exceeding 250 mg/kg for cyclophosphamide or 12 mg/kg for chlorambucil. If further relapses occur, cytotoxic therapy should not be repeated, as potential toxicity may be cumulative. Those patients can be switched to cyclosporin at an initial dose of 4 mg/kg/day in adults and 100 mg/m^2 in children, trying to gradually taper off the drug after 1 – 2 years.

Table 6. Causes of Secondary Focal Glomerulosclerosis

Elderly	Malignancy
Morbid obesity	Familial dysautonomia
Reduced renal mass	IgA nephritis
Reflux nephropathy	Membranous nephropathy
Obstructive uropathy	Segmental hypoplasia
AIDS	Diabetes mellitus
Heroin addiction	Sickle cell disease
Analgesic nephropathy	Transplantation
Hypertension	Oligomeganephronia

Focal Segmental Glomerulosclerosis (FSGS)

FSGS is a clinicopathologic entity characterized by proteinuria, often in nephrotic range, and by focal and segmental sclerosis, which initially predominates in the juxtamedullary glomeruli and then spreads to the outer cortex. The primary form of FSGS affects both children and adults. It may represent an evolutionary stage of MCD. A morphologically similar lesion to FSGS may result from a number of disorders and may create problems of differential diagnosis with the primary form. Most patients with FSGS and the nephrotic syndrome develop renal failure within 10 – 15 years.

Etiology

The current opinion is that MCD and FSGS represent the 2 extremes of the same disease. Both entities are characterized by massive proteinuria as well as by the effacement of the foot processes of epithelial cells on electron microscopy and insignificant deposition of immunoglobulins and complement. The etiology of primary FSGS is unknown as it is for MCD.

Segmental sclerosing lesions may also develop in different clinical instances and can even complicate other glomerular diseases (Table 6). In a number of cases, these secondary forms of FSGS are caused by maladaptive glomerular hemodynamic alterations, leading to glomerular hyperfiltration and hypertension, with eventual development of segmental glomerular scars. FSGS may be a rare complication of obesity and can also develop in heroin addicts and in patients with the aquired immunodefeciency syndrome (AIDS), where the variant of collapsing glomerulopathy seems to be particularly frequent.

Pathology

The initial lesions develop in a portion (segmental) of some glomeruli (focal) (Figure 6). Early lesions affect the deeper juxtamedullary glomeruli. The segmental lesions affect a few capillary loops that stick together, either at the

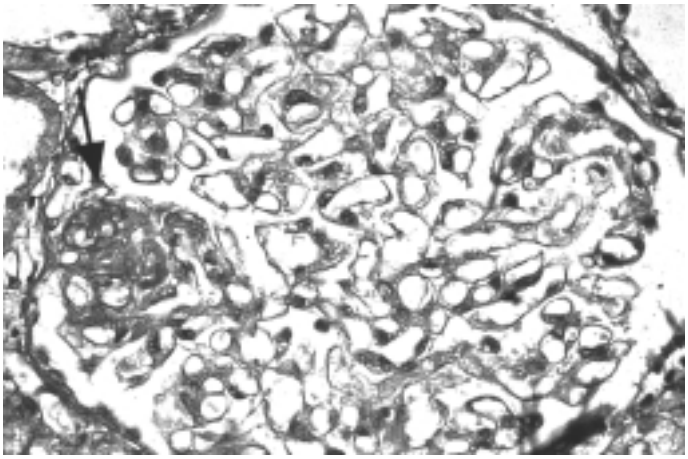

Figure 6. Focal segmental glomerulosclerosis. Typical sclerosis (arrow) of a circumscribed area of the glomerular tuft (500x).

periphery of the tuft (tip lesions) of at the hilum. Hyaline material is often present in the sclerosed areas, which are usually surrounded by a clear halo and always lined by a layer of severely altered and effaced podocytes. Initially, the rest of the tuft and the other glomeruli show only minimal changes, but mesangial hypercellularity may be present. Immunofluorescence is usually negative, but some deposition of IgM and C3 may be seen in the sclerotic areas. Electron microscopy usually reveals diffuse effacement of podocytes and their detachment from the GBM. A form of collapsing glomerulopathy has also been described. It is characterized by glomerular capillary collapse, visceral epithelial swelling, and hyperplasia. It seems to be more frequent in black patients.

Sclerosis progressively destroys the glomerulus, evolving to widespread sclerosis of the whole tuft. With progression of the disease, the lesions extend to the deeper cortex first and then to the outer cortex. Besides the glomerular lesions, there are also tubular and interstitial changes. Initially, there are focal tubular lesions, and foam cells may be seen in the interstitium. In more advanced phases, there is atrophy and interstitial fibrosis of various degree. Interstitial fibrosis is particularly severe in collapsing glomerulopathy, out of proportion to the glomerular process.

Pathogenesis

The pathogenesis of FSGS is similar to that proposed for MCD. The disease could represent a T cell-mediated disorder in which an aberrant clone of T cells secretes a circulating factor that impairs the negative charges of the glomerular structures and probably also of serum albumin and other extrarenal material. Podocytes could be the primary target in FSGS. The initial alterations consisting of an effacement of foot processes may lead to their detachment from the basement membrane. This could result in hyperfiltration, accumulation of subendothelial protein, capillary occlusion, and the formation of synechia between the tuft and the capsule [110]. Massive production of circulating factor(s), genetic predisposition, hyperlipidemia, and hypercoagulation may contribute to the development of FSGS. Another factor that may favor the development of FSGS is an excessive produc-

tion of fibrogenic growth factors. In the animal model, platelet-derived growth factor B and transforming growth factor beta have been implicated in the induction and progression of glomerulosclerosis [90].

The role of circulating factor(s) in eliciting the pathogenesis of FSGS has been further substantiated by experience with renal transplantation. A number of patients who lost their native kidney function because of FSGS show recurrence of proteinuria and the typical lesions of FSGS at renal biopsy after transplantation. Plasmapheresis and/or immunoadsorption with protein A may reduce proteinuria in these cases [39], suggesting that the recurrence of FSGS may be caused by a plasmatic factor. Recently, Savin et al. isolated a circulating factor from patients with recurrence of FSGS after renal transplantation [164]. This factor has a molecular weight of about 50 kd, larger than any known lymphokine, and does not precipitate with immunoglobulins. It might be a nonimmunoglobulin protein or a fragment of an immunoglobulin. However, it is unlikely that this factor neutralizes the anionic-charge barrier, because it is not strongly cationic. Its activity, in very small amounts, might be compatible with that of a cytokine-like molecule that directly injures podocytes.

Clinical Presentation and Course

FSGS accounts for up to 20% of glomerular lesions in children and adults presenting with proteinuria. It is more frequent in the black than in the white population. The clinical presentation is similar at any age, although nephrotic syndrome is more frequent in children and hypertension is more frequent in adults [103]. Some 70 – 90% of patients have a nephrotic syndrome at presentation. Microhematuria is found initially in about half of cases, while macroscopic hematuria is rare. Renal insufficiency may be present in about 20 – 25% of cases at clinical onset.

The disease is usually progressive, and about two-thirds of cases develop end-stage renal disease (ESRD) within 10 – 15 years. A few patients with severe nephrotic syndrome may progress rapidly to renal failure, often associated with arterial hypertension and thrombotic complications. Spontaneous remission of the nephrotic syndrome is exceptional. Complete remission can occur in less than 3% of untreated patients [103].

Several factors may have prognostic significance. The 2 most important clinical features are the level of proteinuria and serum creatinine. Patients with nephrotic range proteinuria reach ESRD within 6 – 8 years in 50% of cases, while the 10-year renal survival is > 90% for patients with non-nephrotic proteinuria [31]. The presence of massive proteinuria, (> 10 g/day, is associated with a particularly poor prognosis, with half of patients reaching ESRD within 3 years [31]. There is also general agreement that impaired renal function at presentation indicates a poor prognosis. Among histologic features, location of sclerotic lesions at hilar pole, glomerular hypertrophy, mesangial hypercellularity, and collapsing glomerulopathy have been considered to be associated with poorer prognosis, by some investigators but not by all. Interstitial fibrosis is universally considered as the strongest prognostic predictor among the histologic features. The response to therapy is also a useful clinical indicator of outcome. A review of the literature showed that < 3% of patients who attained complete remission with therapy developed ESRD by 5 years compared with 55% of nonresponding patients [103]. Even a partial remission is associated with a more favorable course compared to persisting nephrotic syndrome.

Diagnosis

As with most other primary glomerulonephritis, the diagnosis of FSGS also requires renal biopsy. The presence of a single glomerulus with segmental hyalinosis is sufficient to make a diagnosis of FSGS. In the initial phases, however, the diagnosis may be impossible if only the glomeruli of the outer cortex are represented in the histologic sample.

In some instances it can be difficult to recognize whether FSGS is idiopathic or secondary to other diseases or conditions. The forms caused by maladaptive glomerular hemodynamic alterations may be distinguished by the absence of hypoalbuminemia, hypercholesterolemia, and edema in spite of nephrotic levels of proteinuria. Human immunodeficiency virus (HIV) and heroin-associated forms rapidly progress to ESRD within a few months. At renal biopsy, the secondary forms may have large glomeruli with hilar lesions, while tip lesions recall idiopathic FSGS. The presence of mesangial hypercellularity is more typical of the idiopathic form. Probably the most reliable sign for idiopathic FSGS is represented by the effacement of foot processes at electron microscopy.

Treatment

Almost all the studies of FSGS treatment are retrospective. A review of uncontrolled trials reported that 29% of children and 17% of adults [167] treated with glucocorticoids entered complete remission of proteinuria. The majority of these patients were given glucocorticoids for no more than 4 – 8 weeks. Better results have been obtained when patients were given more prolonged glucocorticoid therapy. A review of the literature indicated that 51% of patients treated with prednisone for ≥ 6 months entered complete remission of proteinuria [144]. Most responders maintained normal renal function over time. Unfortunately, no clinical or histologic feature can predict the response to glucocorticoids.

The potential role for immunosuppressive agents is even less clear. The results of retrospective studies suggest that, as with prednisone, the longer the treatment the higher the rate of response, but the cumulative rate of remission is similar to that obtained with glucocorticoids [7]. A randomized trial in children did not show differences between alternate-day prednisone alone or combined with cyclophosphamide for 3 months [184]. On the other hand, at least in adults, the length of remission in responders seems to be longer in patients given cyclophosphamide or chlorambucil. In our own retrospective experience, only 18% of patients who responded to cytotoxic therapy had one or more relapses of nephrotic syndrome vs. 40% of patients who responded to glucocorticoids [7].

Mendoza et al. have proposed an aggressive approach for steroid-resistant children [121a]. Their regimen consisted of high-dose IV methylprednisolone pulses given initially every other day, then at progressively longer intervals for more than one year. The children were also given prednisone, 2 mg/kg every other day. If no response was obtained, cyclophosphamide or chlorambucil was added. Their most recent analysis showed that at the end of a mean follow-up of 6 years, 21 out of 32 children treated were in complete remission, 3 were in partial remission (non-nephrotic proteinuria), 5 had reduced creatinine clearance, and 3 had progressed to ESRD [187]. These results were not confirmed by Waldo et al. who gave a similar regimen to 10 children with FSGS [192]. After 47 months, 6 patients had developed ESRD, 2 had developed renal insufficiency, and the other 2 pa-

tients were still nephrotic. However, 8 of their 10 patients were black, and this may have affected the response rate because blacks may have more severe disease than white patients.

Cyclosporin has also been used in FSGS. A review of the literature found that 40% of patients treated with cyclosporin could be maintained in remission from nephrotic syndrome, the response being similar in children and in adults [103]. Ingulli et al. treated 21 children with cyclosporin for a mean period of 27 months [83]. Proteinuria and cholesterol significantly decreased. When compared with a historical population, the rate of patients who progressed to ESRD was lower in cyclosporin-treated children (24% vs. 78%). This apparent benefit of cyclosporin on proteinuria was also supported by an Italian controlled trial [149]. Nephrotic patients who had not responded to a 6-week course of high-dose prednisone were randomly assigned to supportive therapy or to cyclosporin (5 mg/kg/day in adults and 6 mg/kg/day in children) for 6 months. In the first year, 32% of treated patients entered complete remission, another 27% had partial remission, and only 16% of untreated controls had a partial and transient remission. The mean levels of creatinine clearance did not differ between the 2 groups. However, 66% of patients had a relapse in nephrotic syndrome after cyclosporin was stopped. Thus, a prolonged treatment is needed to avoid nephrotic syndrome. Is this approach safe? Worsening of kidney lesions at repeat renal biopsy has been reported in cyclosporin-treated patients with FSGS [124]. It is not clear however, whether the renal lesions seen on repeat biopsy represent progression of the underlying FSGS in nonresponders or represent cyclosporin toxicity. Whatever the mechanism, the risk of severe tubulointerstitial lesions in patients treated with cyclosporin for FSGS seems to be particularly high when there is an abnormal baseline serum creatinine, when a high proportion of glomeruli with sclerosis is seen at renal biopsy, or when the initial dose of cyclosporin is high. On the basis of the available knowledge, we do not recommend prescribing cyclosporin to patients with abnormal renal function, severe hypertension, tubulointerstitial lesions, or extensive glomerular sclerosis.

In spite of some evidence that a prolonged treatment with glucocorticoids, cytotoxic agents, or cyclosporin may bring about remission and protect renal function in a subset of patients, the optimal treatment regime for FSGS is still unclear. There is general agreement that no specific therapy is needed for patients with asymptomatic proteinuria. There is also consensus about using an 8-week course of high-dose prednisolone in nephrotic patients in order to recognize the few early responders.

What to do with nephrotic patients who do not respond to short-treatment is controversial. Many clinicians do not give any specific therapy, whereas others are quite aggressive and give prolonged steroid and/or cytotoxic treatments. Our practice is that, unless steroid toxicity develops, prednisone should be continued for another 4 – 6 months. One alternative is to give an alkylating agent for 6 months or alternate steroids and an alkylating agent every other month for 6 months, with a schedule similar to that used in membranous nephropathy (MN) [150] in order to reduce the risk of steroid toxicity and to induce a longer remission in responders. If nephrotic syndrome persists, a trial with cyclosporin (initial doses with the new microemulsion 4 mg/kg/day in adults or 100 mg/m^2/day in children) may be offered provided that creatinine clearance and blood pressure are normal and that a recent renal biopsy does not show severe tubulointerstitial lesions. If no improvement of proteinuria is seen within 3 months, cyclosporin should be stopped, as it

Table 7. Causes of Secondary Membranous Nephropathy

Infections	*Association with other diseases*
Malaria	Carcinoma
Schistosomiasis	Non-Hodgkin's lymphoma
Hepatitis B	Hodgkin's disease
Hepatitis C	Chronic lymphocytic leukemia
Syphilis	Systemic lupus erythematosus
Tuberculosis	Autoimmune thyroiditis
Leprosy	Sarcoidosis
Filariasis	Sjögren's syndrome
Streptococcal infection	Sickle cell disease
HIV infection	Diabetes mellitus
Rectal abscess	Dermatitis herpetiform
	Bullous pemphigoid
Drugs and Toxins	Psoriasis vulgaris
Non-steroidal anti-inflammatory drugs	Primary biliary cirrhosis
Captopril	Guillain-Barré syndrome
Penicillamine	Mixed connective tissue disease
Gold	Periaortic fibrosis
Mercury	Myasthenia gravis
Hydrocarbons	Rheumatoid arthritis
Formaldehyde	Renal transplantation

is unlikely that more prolonged treatment will result in remission. In patients who respond, cyclosporin can be continued for another 1 – 2 years at the minimal effective dose. If nephrotic syndrome reappears after stopping cyclosporin, a renal biopsy may be repeated before deciding whether or not therapy with cyclosporin should be continued.

Membranous Nephropathy (MN)

MN is a glomerular disease characterized clinically by proteinuria and histologically by a diffuse thickening of the GBM due to deposition of subepithelial immune-complexes. MN is idiopathic in the majority of cases, but in some instances it is secondary to well-defined causes. The course of the disease may be variable. Some patients maintain normal renal function with or without remission of proteinuria, but others progress to renal failure or die from complications related to the nephrotic syndrome.

Etiology

Exceptionally, MN may affect siblings. An association between MN and human leukocyte antigen (HLA)-DR3 antigen has been reported by many studies in white patients. In Japanese patients there is an increased incidence of HLA-DR2 [174].

In most cases of MN no etiological factor can be identified. However, in about one-fourth to one-third of cases, MN is associated with identifiable causes (Table 7). The overall prevalence of secondary MN appears to be

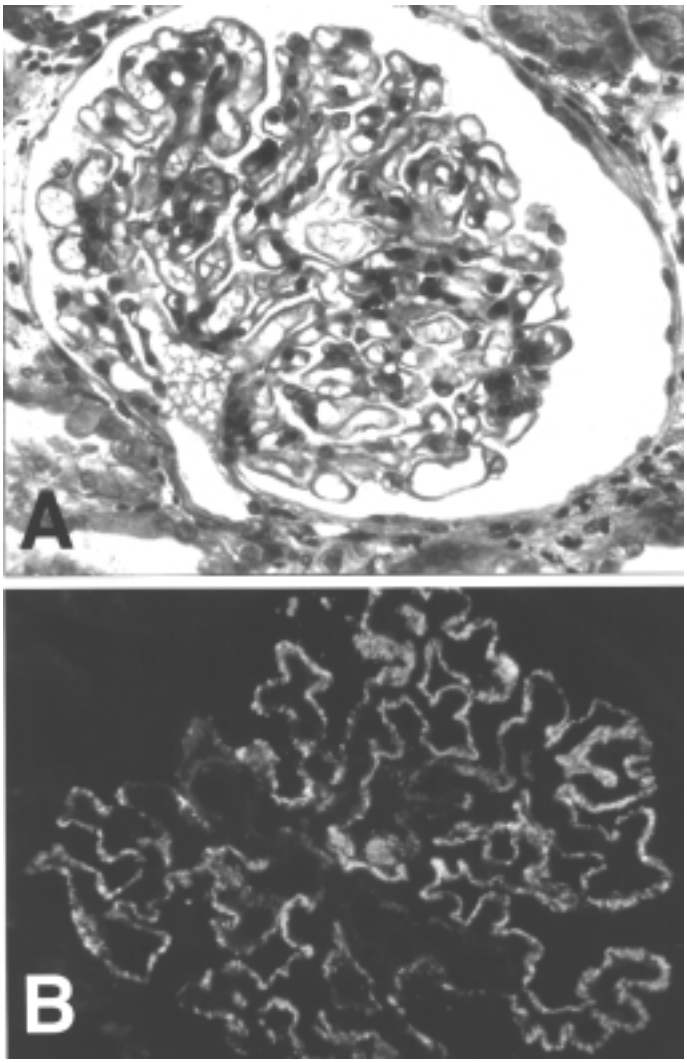

Figure 7. Membranous nephropathy. A: diffuse and homogeneous thickening of the glomerular capillary walls (500x). B: granular deposition of IgG as seen by immunofluorescence (500x).

higher in children and in older adults. Worldwide, malaria and schistosomiasis are the most common causes of secondary MN. Hepatitis B and C are also frequent causes of MN, particularly in endemic areas [106]. MN may be the first manifestation of SLE and may precede serological abnormalities by several years. In some 10% of patients, MN is associated with malignancy. In 40 – 45% of these cases, renal disease may antedate the initial manifestations of the underlying cancer by months or even years [29]. In a number of cases, MN can be secondary to toxic agents or drugs. Penicillamine and gold are 2 well-known causes of MN, but NAIDs are probably the most frequent etiologic drugs of secondary MN. In a recent report, these drugs were responsible for 10% of stage I MN [155]. Recognition of the toxic agent or drug as a cause of MN is important because proteinuria usually remits after the removal of the offending agent.

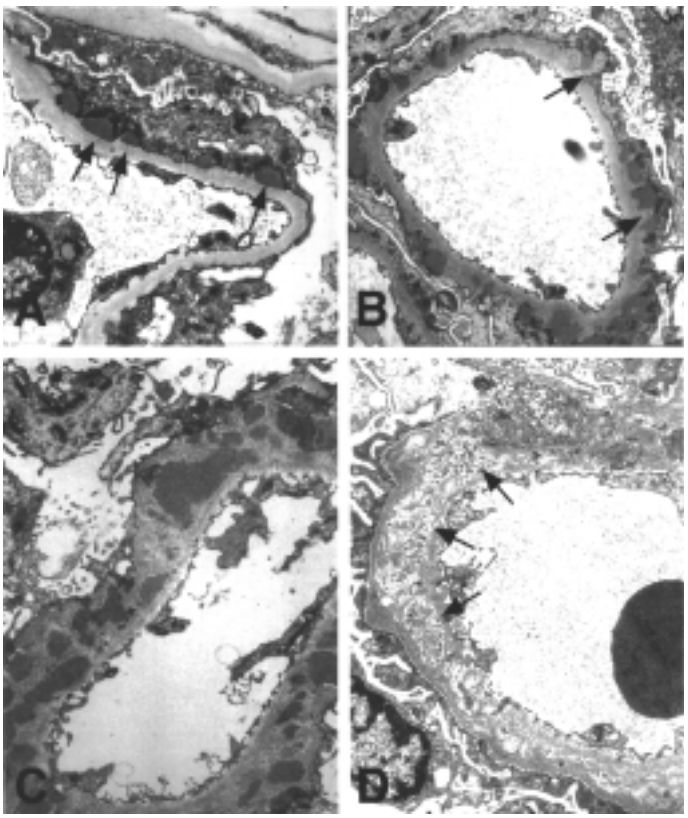

Figure 8. Membranous nephropathy as seen by electron microscopy. A: stage I, with few electron-dense deposits (arrows) on the subepithelial side of the GBM. B: stage II, with projections of the GBM (arrows) around the electron-dense deposits. C: stage III, with electron-dense deposits incorporated within a thickened GBM. D: stage IV, with partially reabsorbed deposits (arrows) and irregular thickening of the GBM. (7,000 – 8,000x)

Pathology

MN is characterized by typical alterations of the GBM caused by subepithelial deposition of immune deposits (Figure 7). Ehrenreich and Churg described 4 glomerular stages of the disease (Figure 8) [52]. In stage I, the glomeruli appear almost normal at light microscopy, but at electron microscopy there are small, spaced, subepithelial electron-dense deposits and diffuse foot process fusion. Immunofluorescence shows diffuse granular deposits of IgG and C3 along the capillary loops. In stage II, light microscopy shows a diffuse, uniform thickening of the GBM, with characteristic spikes on silver stain. By electron microscopy, these are due to projections of the GBM. The deposits are larger, more uniform, and numerous. In stage III, the deposits are incorporated within the GBM, which appears thickened at light microscopy. In stage IV, the GBM is markedly but irregularly thickened. By electron microscopy there is rarefaction of deposits due to resorption. The intensity of the deposits at immunofluorescence may be rather low. These stages are common to all forms of MN, but in secondary forms subendothelial deposits as well as mesangial proliferation may be present. They are not usually found in idiopathic MN. The finding of IgA or C1q by immunofluorescence also suggests a secondary MN.

Although some investigators have found that patients with stage I – II glomerular lesions are unlikely to develop renal failure [52], others did not find any correlation between the glomerular stage and the renal out-

come [97, 150, 196]. An unfavorable prognostic role has been attributed to the finding of a superimposed focal glomerulosclerosis [191]. There is general agreement, however, that interstitial fibrosis and tubular atrophy, rather than glomerular changes, are the histologic findings more strictly associated with a poor prognosis [97, 150, 196].

Pathogenesis

As shown by immunofluorescence and electron microscopy, MN is characterized by the subepithelial deposition of immune complexes. Two hypotheses regarding the immune deposits formation have been considered. First, circulating immune complexes of intermediate size escape phagocytosis from the reticuloendothelial system, pass the GBM, and deposit in the subepithelial space. This mechanism might be operating in some cases of secondary MN. Circulating complexes have been detected in MN associated with SLE, hepatitis B, or neoplasia; and in some cases the antigen has been eluted from glomeruli [183]. However, such a pathogenesis is unlikely in idiopathic MN, as a number of clinical studies failed to detect circulating immune complexes. Second, immune complexes could form in situ by antibody reacting with antigens planted in the glomeruli or with endogenous glomerular antigen.

The Heymann nephritis model has been largely used to understand the pathogenesis of idiopathic MN. There are 2 models of Heymann nephritis. Both of them lead to an autoimmune-mediated glomerulonephritis that has functional and immunopathologic features similar to human idiopathic MN. Active nephritis is induced by immunization of susceptible strains of rat with crude proximal tubular brush border extract. The passive Heymann nephritis is induced by injecting antibodies against this extract. Two main antigenic determinants have been identified in Heymann nephritis: megalin and receptor-associated protein. Megalin, previously called gp 330, is a member of low-density lipoprotein receptors located in the brush border of tubular cells and, in lower amounts, in glomerular epithelial cells. The receptor-associated protein binds to megalin and may serve as its intracellular chaperon [54]. There is now evidence that in Heymann nephritis subepithelial deposits do not derive from trapped circulating immune complexes but are caused by in situ complex formation [95]. Antibodies penetrate the GBM and bind to antigens located at the base of the epithelial cells. The immune deposits grow in size by repeated cycles of immune complex formation and new formation of megalin. A similar mechanism is thought to be operating in human idiopathic MN, although the target antigen has yet to be identified.

The subepithelial deposition of immune complexes activate the complement system with formation of the C5b – C9 complex (membrane attack complex). This results in release of potential inflammatory mediators such as prostaglandins, oxidants, and proteinases leading to damage of the glomerular epithelial cells and altered glomerular barrier function [36]. An important role in the progression of renal disease has been attributed to cytokines, particularly transforming growth factor β, which can stimulate the synthesis of collagens, fibronectin, and proteoglycans and contribute to the accumulation of extracellular matrix material within the damaged kidney [18, 173].

Clinical Presentation and Course

Idiopathic MN is rare in children while it occurs in adults usually between 30 and 50

years. In people aged > 60 years MN has an annual incidence 2.5 fold higher than in younger population [175]. Overall there is a predominance of males at 2 : 1 ratio [79]. Proteinuria, usually non-selective, is the hallmark of the disease. Some 70 – 80% of patients have a nephrotic syndrome at presentation and others may become nephrotic later. Microscopic hematuria is found in about half of patients. Gross hematuria and red blood cell casts are rare. Arterial hypertension and renal dysfunction may be present at clinical onset.

Idiopathic MN may have a variable outcome. Some patients may show spontaneous reduction or even disappearance of proteinuria over time, others may remain nephrotic with stable renal function, and others may slowly progress to ESRD or die from extrarenal complications. It is difficult to assess the natural course of the disease and the relative importance of these events because the inclusion criteria in the available studies were very different. Moreover, most studies included both treated and untreated patients, and the length of follow-ups was quite different. Some studies that considered both patients with and without nephrotic syndrome at presentation and followed for 5 – 6 years concluded that MN is a benign disease with a high rate of spontaneous remission [32, 50, 168]. Other series that included only nephrotic patients with longer follow-up reported a 10-year kidney survival of around 50% [51, 81].

A number of studies tried to identify which clinical and/or histologic factors could predict the renal course at presentation. The conclusions were often contradictory. With univariate analysis, male sex, age > 50 years, HLA-DR3 genotype, superimposed glomerulosclerosis, heavy proteinuria, and arterial hypertension at presentation were found to be associated with a poorer prognosis by some investigators but not by others. When multivariate analyses were performed, the factor more strongly associated with renal failure was the presence of interstitial fibrosis and tubular atrophy at initial renal biopsy [97, 150, 196].

More information may be obtained by the follow-up of the patients. It has been pointed out that most patients who progress to renal failure have some increase in plasma creatinine after 2 – 3 years [195]. Pei et al. described a model that predicted outcome in a semiquantitative fashion by evaluating the persistence of certain levels of proteinuria over time [140]. The risk of chronic renal failure was 66% for patients with proteinuria ≥ 8 g/day for at least 6 months, 55% when proteinuria exceeded 6 g/day for ≥ 9 months, and 47% for proteinuria > 4 g/day for ≥ 18 months. These data were recently validated by extending the study to 360 MN patients from 3 different countries who were followed for a mean of > 6 years [34]. Complete remission of proteinuria, whether spontaneous or induced by treatment, probably represents the most reliable clinical predictor of a favorable outcome in the long term. The published data show that only 1 of 157 patients who attained complete remission had to undergo dialysis [146].

It is even more difficult to predict which patient may have spontaneous remission of proteinuria. We studied the influence of several factors on the development of remission. Among the numerous variables taken into consideration, only treatment with steroids and cytotoxic agents and glomerular stage I – II at initial biopsy significantly increased the probability of remission [148].

Patients with MN are also exposed to extrarenal complications. Thrombotic events are frequent in nephrotic patients. Among primary glomerulonephritides, idiopathic MN has the highest risk of renal vein thrombosis. This may occur in about 10% of patients and is frequently complicated by pulmonary em-

boli [203]. Deep vein thrombosis may develop in about 11% of patients with MN [10]. Arterial occlusion may also complicate the course of this disease. MacTier et al. reported 14 cases of arterial occlusion in 37 untreated patients with MN followed for a mean period of 64 months [114].

Diagnosis

The diagnosis of MN may be suspected on clinical grounds but requires renal biopsy to be confirmed. After the histologic diagnosis has been obtained, efforts should be made to identify possible causes of MN. In most instances, a thorough history and clinical examination are sufficient to recognize the secondary cause. Because hepatitis may be occult, a serological screening for hepatitis virus B and C (HBV and HCV) is mandatory. Two underlying diseases may pose diagnostic problems: SLE and neoplasia. MN may be the first manifestation of SLE and may precede serologic abnormalities even by years. The diagnosis of lupus MN may be suspected whenever IgA and C1q as well as subendothelial and mesangial deposits are found, but only the presence of virus-like particles or tubular basement deposits at electron microscopy may be considered to be specific for SLE [87]. In some 10% of cases, MN may be associated with cancer and in 40 – 45% of patients with cancer, neoplasia may antedate the initial manifestations of cancer by months or years [29]. It is still debated how extensively an underlying cancer should be investigated. We feel it is appropriate to recommend a stool guaiac examination, renal ultrasonography, chest X-ray, and prostatic antigen. Mammography and colonoscopy should also be performed in patients older than 50 years. Aged patients should be closely followed because neoplasia is more frequent in the elderly and may be undetectable on initial screening.

Treatment

Patients with idiopathic MN and subnephrotic proteinuria do not need any specific treatment because the risk of developing renal failure is minimal [50, 51]. Moreover, these patients are asymptomatic and are not exposed to the risk of nephrotic complications. The only treatment we suggest is the use of ACE inhibitors or antagonists of Ang II receptors that may reduce proteinuria.

Whether or not patients with nephrotic syndrome should receive specific treatment is still a matter of debate. A meta-analysis of controlled studies with glucocorticoids concluded that these agents are of no benefit either in favoring remission or in improving kidney survival [79]. Controlled trials with cytotoxic agents gave conflicting results although generally showing a favorable effect on proteinuria [146]. Unfortunately, most studies were performed on small groups of patients and follow-ups were short. A combination of steroids and chlorambucil was assessed in an Italian controlled trial. Patients with idiopathic MN and nephrotic syndrome were randomly assigned to receive symptomatic therapy or methylprednisolone (1 g for 3 days IV, then 0.4 mg/kg/day orally for 1 month) alternated every other month with chlorambucil (0.2 mg/kg/day for 1 month) for 6 months. The actual probability of surviving without developing ESRD at 10 years was significantly better in patients given steroids and chlorambucil (92%) than in untreated controls (60%). The slope of the reciprocal of plasma creatinine was also significantly better in treated patients than it was in controls. The probability of having complete or partial re-

mission as a first event was significantly better for treated patients (88% vs. 47%). Among the numerous variables taken into consideration, only treatment was significantly associated with remission. At the last follow-up visit 17 of 42 treated patients vs. 2 of 39 untreated patients were without proteinuria. Four of 41 patients had to stop therapy because of adverse events, which were reversible. No disquieting morbidity was observed in the long term [151]. On the basis of available studies, we feel that a 6-month regimen alternating glucocorticoids with an alkylating agent (either chlorambucil or cyclophosphamide) offers good chances of obtaining remission and preserving renal function. Some 10% of patients may develop side effects that are usually reversible. Leukopenia and infection are the most frequent side effects. Thus, it is recommended that the blood cell count be checked at least every 10 days during cytotoxic treatment. The alkylating agent should be halved when leukocytes fall < 5,000/mm^3 or stopped if they fall < 3,000/mm^3. A main concern with the use of cytotoxic agents is the possible development of cancer. We pooled all patients who were treated with chlorambucil in our controlled studies. We observed 3 cases of malignancy (one probably preexisting) out of 662 patient-years, with a cumulative risk of 4.5/1000 per year similar to the 4.3/1000 per year observed in the white general population. Thus, it would seem that there is little if any oncogenic risk of a cumulative treatment of 3 months with chlorambucil.

On the basis of these results, we feel that patients with MN and persisting nephrotic syndrome can benefit from a 6-month course with steroids alternated with a cytotoxic drug. In patients who have contraindications to glucocorticoids, a 6- to 12-month course with cyclophosphamide alone may be tried, although the oncogenic risk as well as the bladder and gonadal toxicity increase with more prolonged cytotoxic treatment. Cyclosporin can also be used. In a review it was found that of 73 adults with MN treated with cyclosporin, 20% entered complete remission and 25% had partial remission [123]. Remission was usually obtained within 6 months. However, most patients relapse after cyclosporin is stopped.

Table 8. Therapeutic Decisions in Patients with Idiopathic Membranous Nephropathy and Slowly Progressive Renal Insufficiency

	Treat	Do not treat
Pl. creatinine	< 5 mg/dL	> 5 mg/dL
Ultrasonography		
size	Normal	Reduced
Hyperechogenicity	+/++	+++
Renal biopsy		
Tubulointerstitial lesions	+/++	+++
Immune deposits	yes	No

In patients with renal insufficiency, a rapid decline of renal function may be caused by an acute renal vein thrombosis, by a superimposed extracapillary glomerulonephritis, by an interstitial nephritis caused by diuretics, nonsteroidal anti-inflammatory drugs or other drugs, or simply by dehydration. Thus, whenever a sudden increase in plasma creatinine occurs, efforts should be made to recognize and appropriately treat any possible superimposed complications. For patients with slowly progressive renal failure, the indication to treatment depends on the degree of renal dysfunction, the characteristics of kidney at ultrasonography, and the histologic findings at renal biopsy (Table 8). In fact, as patients with renal insufficiency are more exposed to the risk of side effects caused by glucocorticoids and cytotoxic drugs, treatment should be lim-

ited to those cases having actual chances of improving. Several therapeutic approaches have been used. The best results have been obtained with 1 – 2 years of cyclophosphamide associated with low-dose prednisone [27, 88] or with a 6-month course with methylprednisolone and chlorambucil [26, 119, 157].

Most investigators reported numerous and sometimes severe treatment side effects in patients with renal insufficiency. In order to reduce iatrogenic morbidity, the doses of the chosen agents should be reduced. If a schedule based on prolonged cyclophosphamide is chosen, the daily dose should not exceed 1.5 mg/kg/day. If the methylprednisolone-chlorambucil regimen is preferred, the pulses of methylprednisolone should be 0.5 g each, and the daily dosage of chlorambucil should be around 0.1 mg/kg.

Membranoproliferative Glomerulonephritis (MPGN)

MPGN or mesangiocapillary glomerulonephritis is a disease characterized by mesangial hypercellularity and proliferation with broadened capillary loops. Four types of primary MPGN have been described. The clinical expression of these types is similar, with nephritic or nephrotic syndrome, hypertension, and often hypocomplementemia. Some 50 – 60% of patients develop renal failure within 10 years from clinical onset. The treatment of idiopathic MPGN is still controversial.

Table 9. Disorders Associated with Membranoproliferative Glomerulonephritis

Autoimmune diseases	*Neoplasias*
Lupus nephritis	Lymphomas
Mixed cryoglobulinemia	Leukemia
Sjögren syndrome	Nephroblastoma
Sarcoidosis	Light-chain disease
Complement deficiencies	
Rheumatoid arthritis	*Miscellaneous*
	Sickle cell disease
Infectious diseases	Castleman's disease
Hepatitis B and C	Thrombotic microangiopathy
Visceral abscesses	
Shunt nephritis	
Quartan malaria	
Schistosomal infection	
Mycoplasma infection	
HIV	

Etiology

Idiopathic MPGN is a rare disease. The incidence of type I MPGN is decreasing in the developed world but remains relatively common in underdeveloped countries. The incidence of type II has remained unchanged. Children and adolescents are affected more frequently than adults, but there is not a substantial difference between sexes. It has been reported that the haplotype HLA-B8, DR3, SC01, GL02 is more frequent in patients with type I MPGN [197]. Some familial cases of type I and II have also been described. An association with partial lipodystrophy has been reported in some cases of type II MPGN. Among the 4 types of MPGN, type I is by far the most common, accounting for almost 80% of cases; type II represents 15 – 20% of cases; type III accounts for < 5% of cases; and type IV is very rare. A histologic pattern of MPGN may be observed in a number of autoimmune diseases, chronic infections, paraproteinemias, and neoplasia (Table 9). Lupus nephritis and mixed cryoglobulinemia are the most frequent causes of secondary MPGN.

Table 10. Main Histological Features in Membranoproliferative Glomerulitis

Common features: increase in mesangial cells and matrix, thickening of capillary walls.

	Location of deposits	Immunofluorescence pattern
Type I	Mesangial and subendothelial	IgG and C3 (C1q – C4) granular pattern
Type II	Mesangial and dense intramembranous	C3 (early complement components and IgG usually negative)
Type III – IV	Mesangial, subepithelial and subendothelial	C3 (early complement components and IgG usually negative)

Pathology

The 4 major types of MPGN have been identified with different findings, particularly on electron microscopy and immunofluorescence. Light microscopy is similar in each type with increase in mesangial cells and matrix and thickening of the capillary walls (Table 10).

Type I is also called subendothelial MPGN (Figure 9A). In type I the cellular increase is due to mesangial cells and infiltrating neutrophils. The thickening of the capillary wall is caused by the interposition of mesangial cells and matrix as well as neutrophils into the capillary wall. In many cases the silver staining shows a typical aspect of double contour ("tram-track"), caused by the staining of the true basement membrane and of a false membrane produced by mesangial interposition. The mesangial increase may accentuate the lobular form of the glomeruli leading to a lobular appearance. A nodular form has also been described. It is characterized by centrolobular sclerosis associated with dilation of glomerular capillaries. Although the changes are generally diffuse, focal and segmental abnormalities have been described in a few cases. Immunofluorescence shows granular deposits of C3 (Figure 9B) often associated with IgG and less frequently IgM. C1q and C4 may be present in about half of cases while properdin is always present. These components deposit along the internal side of the capillary walls and less prominently in the mesangium. In a few cases there is a lobular pattern. The deposits outline a lobulated tuft while there are no deposits in the mesangium. Electron microscopy confirms the lesions observed by light microscopy and shows typical electron-dense deposits mainly located in the subendothelial areas (Figure 9C).

Type II MPGN is also called dense deposits disease. The cardinal feature is a ribbon-like aspect of the basement membranes of glomeruli, tubules, peritubular capillaries, and Bowman's capsules (Figure 9D). Subepithelial humps similar to those seen in post-streptococcal glomerulonephritis may be seen in about one-third of cases. In some patients, however, the dense deposits may be missed at light microscopy. Immunofluorescence shows linear staining of C3 along the capillary walls and bright granules in the mesangial regions. Deposits of C1q, C4, properdin, and IgG are rare. The intramembranous deposits are negative for immunofluorescence. Electron microscopy clearly shows dense amor-

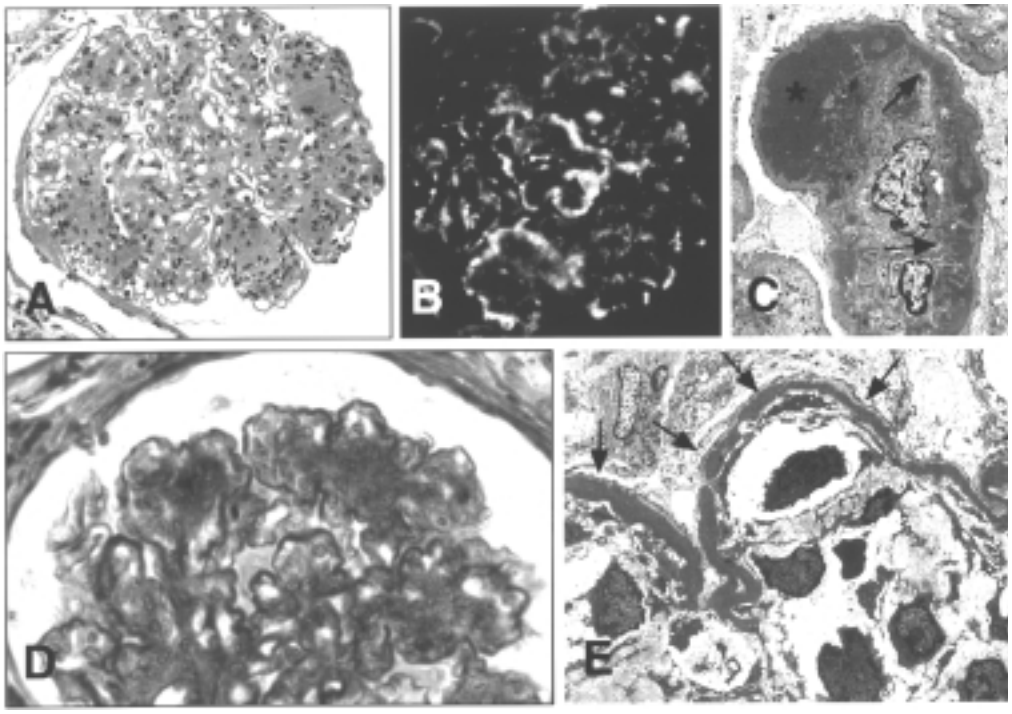

Figure 9. Membranoproliferative glomerulonephritis. A: type I MPGN with a typical lobular appearance (400x). B: typical coarse deposits of C3 along the glomerular capillary walls as seen by immunofluorescence (500x). C: large (*) and small (arrows) subendothelial electron-dense deposits as seen by electron microscopy (3,500x). D: type II MPGN with the typical ribbon-like appearance of the glomerular capillary loops (630x). E: type II MPGN with continuous electron-dense deposits in the context of the GBM as seen by electron microscopy (3,500x).

phous osmiophilic deposits in the basement membrane and in the mesangium (Figure 9E). The deposits are not continuous, and some capillary walls may appear normal.

Type III MPGN is also called mixed membranous and proliferative glomerulonephritis. The main lesions are similar to those observed in type I MPGN. However, the deposits are subepithelial rather than subendothelial, with interspersed projections of basement membrane. Immunofluorescence shows C3 but no or minimal deposition of immunoglobulins.

Type IV MPGN is characterized by a disruption of the basement membranes. Both subendothelial and subepithelial deposits may be seen. Whether types III and IV should actually be considered as separate entities or variants of type I is still controversial.

Pathogenesis

The findings of immunofluorescence and electron microscopy strongly support the hypothesis that type I MPGN is an immune-complex mediated disorder. The demonstration of circulating complexes and the frequent hypocomplementemia with a classic activation pathway are also consistent with this hypothesis. However, the nature of the anti-

gen(s) involved remains unknown. Also, it is unclear whether the complex deposition is actually the triggering event leading to endothelial damage, mesangial activation and expansion, and peripheral interposition of mesangial material.

The pathogenesis of type II MPGN is even less understood. A role for immune complexes can be excluded, because immunoglobulin deposits are usually absent and dense deposits do not show any of the typical characteristics of immune-complex deposits. The frequent recurrence of the disease after transplantation also excludes a primary defect of the GBM. Rather, it suggests that type II MPGN is a systemic disorder that causes the aggregation of basement membrane-like material on renal basement membranes. In patients with type II MPGN, a circulating IgG called C3 nephritic factor can activate the alternative pathway of complement. This has raised the hypothesis that complement abnormalities may play a primary pathogenetic role. However, despite much study the importance of serum C3 nephritic factor remains undefined, as there is no relationship between the serum levels of C3 nephritic factor or complement and the clinical course. It is possible that hypocomplementemia may represent the consequence rather than the cause of the capillary wall damage. The increased consumption of complement could be triggered by complement binding to the abnormal basement membranes. The presence of large deposits of lipids in the dense deposits suggests that this material is the result of a deposition of substances of extrarenal origin [130]. Immunological mechanisms, still poorly elucidated, might contribute in amplifying the damage to the membranes and in sustaining hypocomplementemia.

The pathogenesis of types III and IV MPGN is also unclear. The presence of discrete deposits on electron microscopy may suggest an immune-complex mechanism, although there are minimal deposits of immunoglobulins on immunofluorescence.

Clinical Presentation and Course

MPGN may present with the abrupt onset of hematuria, heavy proteinuria, and hypertension sometimes preceded by an infection of the upper respiratory tract. In other cases, the disease is discovered because of the insidious appearance of edema or because of the finding of microscopic hematuria and proteinuria on a routine urinalysis. At least half of patients have a nephrotic proteinuria, one-third have arterial hypertension, and 20% have renal insufficiency at presentation. Hematuria and cellular and granular casts are usually found on urinalysis. Hypocomplementemia is present in about 50% of cases with type I MPGN and in 70 – 80% of cases with type II MPGN. In type I, complement is activated by the classic pathway, possibly in response to the immune-complex formation. As a consequence, there is a moderate reduction of serum C3 associated with low levels of the early components of complement, such as C4. In type II, there is an activation of the alternate pathway, probably caused by C3 nephritic factor, which induces the cleavage of C3. In the serum of these patients, the early components of complement are normal but there is a profound reduction of C3.

Most patients have a progressive course. This is usually slow so that many patients show normal or subnormal renal function in the first few years after clinical onset. By 10 years, however, some 40% of patients with type I and 50% with type II MPGN [31, 64] have reached ESRD. In a few patients there is a rapidly progressive course. A superimposed crescentic glomerulonephritis may be seen at renal biopsy in some of these cases. Other

patients may show acute nephritic episodes triggered by infections of the upper respiratory tract, with rapid deterioration of renal function, which is sometimes reversible.

Several clinical and histologic features affect the likelihood of progressing to renal failure. A large amount of proteinuria, arterial hypertension, and increased serum creatinine at presentation are usually associated with a poor prognosis [37]. On the contrary, the pattern of complement levels and their fluctuations have little impact on prognosis. As for other glomerular diseases, severe tubulointerstitial lesions at initial renal biopsy represent the most important prognostic factor among morphologic features. Superimposed crescents may also affect the prognosis adversely.

Diagnosis

The acute nephritic presentation of MPGN may mimic poststreptococcal glomerulonephritis (PSGN), lupus nephritis, IgA nephritis, and cryoglobulinemic nephritis. A differential diagnosis may be made on certain clinical clues. Distinguishing between MPGN and PSGN may be difficult because both disorders can be triggered by upper respiratory infections. Usually in PSGN there is a longer free interval between infection and the first renal signs, the nephrotic syndrome and renal failure are more rare, and hypocomplementemia returns to normal within 6 – 8 weeks.

If present, hypocomplementemia can rule out a suspicion of IgA nephritis. Serum cryoglobulins may be found in idiopathic MPGN, but the presence of purpura, arthralgias, positivity for HCV, and high levels of RF allow the diagnosis of mixed cryoglobulinemia. The simultaneous decrease of serum C3 and C4 indicates an activation of complement through the classic pathway, which can be found in type I MPGN, while low levels of C3 with normal serum levels of C4 express an activation by the alternative pathway characteristic of type II MPGN.

In most cases, however, the diagnosis of MPGN can be made only by renal biopsy. The histologic material should be investigated by optic microscopy, immunofluorescence, and electron microscopy to obtain an adequate classification. An extensive search for underlying disease should be done to evaluate whether MPGN is primary or secondary. This should include anti-DNA antibodies, cryoglobulins, serum and urine protein immunoelectrophoresis, serology for hepatitis B and C, and in older patients investigations for malignancy. Blood cultures should be performed in case of bacterial infections [64].

Treatment

Several therapeutic approaches have been tried in MPGN. The Cincinnati group for many years has used long-term, high-dose, alternate-day prednisone therapy in children. Prednisone is begun at a dose of 2 – 2.5 mg/kg (maximum dose 80 mg) every other day and slowly reduced it to 1 – 1.5 mg/kg every other day after 2 years and 0.2 – 1.0 mg/kg every other day after 4 years. Of 71 pediatric patients, survival at 10 and 20 years from the time of diagnosis was 82% and 56%, respectively. Steroids were usually well tolerated [120]. The efficacy of this regimen has been evaluated by a randomized, placebo-controlled trial organized by the International Study of Kidney Diseases in Children [183b]. A total of 80 children with primary MPGN were randomly assigned to receive placebo or prednisone 40 mg/m^2 every other day for a mean duration of 41 months. Only 12% of placebo patients had stable renal function over the first 10 years vs. 61% of treated patients. However, the difference was not significant. Repeat re-

nal biopsy showed no important differences between treated and placebo patients. Unfortunately, the power to detect substantial differences was small. Many patients stopped either treatment or placebo because of renal failure or side effects. Differences in renal function were observed only after 90 months, but at that time only 18 patients were still under observation. Other uncontrolled studies suggested that the results with glucocorticoids in children may be improved if treatment is started early after diagnosis and if it is tailored to the severity of the disease. Ford et al. used IV methylprednisolone pulses followed by high-dose oral prednisone in patients with creatinine clearance < 50 mL/min, while low-dose alternate day prednisone was given in children with normal renal function [59]. The average creatinine clearance increased from 78 to 126 mL/min after a mean follow-up of 6.5 years and a mean duration of treatment of 38 months. Repeat renal biopsies showed reduced inflammatory activity in the majority of cases. The results with glucocorticoids in adults are limited. An analysis of the available trials concluded that glucocorticoids do not show any benefit in adults [49].

Immunosuppressive drugs, alone or in combination with anticoagulants or indomethacin, have been claimed to be of benefit in some noncontrolled studies. However, a controlled trial failed to show favorable effects of a combination of cyclophosphamide with oral anticoagulants and dipyridamole [32].

Donadio et al. found that a combination of aspirin (975 mg/day) and dipyridamole (225 mg/day) could significantly delay the deterioration of renal function over the first 4 years, although there was no modification of proteinuria or hematuria [46]. However, this advantage was lost in the long-term, the 10-year renal survival being 49% in treated patients and 41% in untreated patients [49].

In summary, the treatment of MPGN remains elusive. We do not recommend any specific treatment in patients with normal renal function and asymptomatic proteinuria. A trial with alternate-day glucocorticoids may be attempted in patients with severe nephrotic syndrome who usually have a bad prognosis. Oral prednisone may be given at a dose of 2 mg/kg every other day for 2 months with gradual decrease in the following period. If proteinuria does not vary within 4 – 6 months, the steroid should be stopped. If there is considerable reduction of proteinuria, the steroid may be continued at the minimal effective doses. In patients with rapidly progressive decline of renal function, a renal biopsy should be obtained. In the presence of an extracapillary glomerulonephritis or a superimposed interstitial nephritis, an aggressive treatment with high-dose IV methylprednisolone pulses, oral prednisone, and cyclophosphamide may obtain a recovery of renal function in several patients.

IgA Nephritis (IgAN)

IgAN, also called Berger disease [13], is the most common primary glomerulonephritis in the world. It may present with macroscopic hematuria or with microscopic hematuria and mild proteinuria. In other cases, the diagnosis is made on the occasion of the discovery of renal insufficiency. In spite of intensive investigation, the pathogenesis of IgAN is unclear, and there is not yet a definite treatment.

Etiology and Epidemiology

The cause of IgAN is still unknown. Even though in a number of cases it may be associ-

Table 11. Main Conditions Associated with Mesangial IgA Nephropathy

Primary
IgA nephropathy (Berger disease)
Systemic
Henoch-Schönlein purpura
Secondary
Chronic liver disease
Crohn's disease
Celiac disease
Dermatitis herpetiformis
Psoriasis
Episcleritis
Sjögren syndrome
IgA monoclonal gammopathy
Carcinomas (lung, pancreas, mucin-secreting)
Mycosis fungoides
Ankylosing spondylitis
Reiter's disease
Leprosy
Toxoplasmosis
HIV infection
Thin basement membrane disease

ated with other conditions (Table 11), IgAN is mainly a primary renal disease. In about 50% of patients, IgAN presents after upper respiratory infections, either viral or bacterial. Much less frequently IgAN may be preceded by other infections (e.g. intestinal or urinary) or by surgery, vaccination, or heavy physical efforts. In the remaining cases, precipitating factors cannot be found.

IgAN is ubiquitous, but its prevalence varies in different geographical areas. Of all patients with glomerulonephritis, IgAN constitutes approximately 8% in Canada, 12% in the United States, 20 – 27% in Southern Europe, 40% in Japan, and > 50% in Singapore [82]. At least in part, this distribution reflects different attitudes towards the screening of renal diseases and different indications for renal biopsy in patients with only mild urinary changes.

IgAN can affect any age, but the highest prevalence is in the second and third decades of life. Males are more frequently affected than females, with a ratio ranging from to 2:1 to 6:1 according to race. All races are affected, but IgAN is less common in blacks than in Caucasians and Asians.

Occasionally, IgAN can affect several members of the same family [91, 172]. In some families one member can suffer from IgAN and another from Henoch-Schönlein purpura (HSP) [121], which is an additional element in favor of the common pathogenesis of the 2 conditions. Immunogenetic studies have shown that IgAN may be associated with different HLA antigens, even in the same country [165].

Pathology

By light microscopy, a large spectrum of patterns can be found, from almost normal kidneys to diffuse proliferative or sclerosing forms. In most cases the typical pattern consists of focal and segmental proliferation of mesangial cells associated with expansion of the mesangial matrix (Figure 10A). Although small epithelial crescents are frequent, a true crescentic form is rare [1]. In a minority of cases focal-segmental glomerulosclerosis can be seen [69]. In patients with gross hematuria, acute tubular necrosis (ATN), thought to derive from tubulotoxic effects of erythrocyte components, can superimpose to the glomerular lesions [56, 98]. At a cellular level, increased numbers of macrophages can be observed in the glomeruli in the initial phases of the disease [132]. Increased numbers of monocyte/macrophages and T lymphocytes as well as myofibroblasts can be found in the

interstitium, especially in progressive cases [3, 68].

Immunohistology is mandatory for the diagnosis of IgAN. IgA is the dominant glomerular antigen, which is present in *all* glomeruli, including those that are normal by light microscopy. In typical cases, IgA deposits located in the mesangium appear as confluent masses with moderate-to-high intensity stain (Figure 10B). Extension to the paramesangial areas is frequent, but deposits in peripheral areas of the glomerular capillaries are less common. Other immunoglobulins such as IgG and IgM can also be found, the latter being observed especially in the areas of sclerosis. C3 is almost as frequent as IgA, with a similar pattern but lower intensity stain. C4 and C1q are negative, which is useful to distinguish IgAN from other proliferative nephritis [84]. Fibrinogen can also be observed in the mesangium.

The IgA deposited in the glomeruli belongs to IgA1 subclass [131] and contains mostly lambda light chain [105]. The finding of the J chain, which is a subunit of dimeric and polymeric immunoglobulins, suggests that the glomerular IgA is polymeric [126].

Electron microscopy shows mesangial cell proliferation, increased mesangial matrix, and electron-dense deposits in the mesangium. Electron-dense deposits can also be seen at the periphery of the glomerular capillaries, either in the subendothelial or subepithelial location, often in association with irregularities of the GBM. Some patients have abnormally thin basement membrane (< 264 nm) [14].

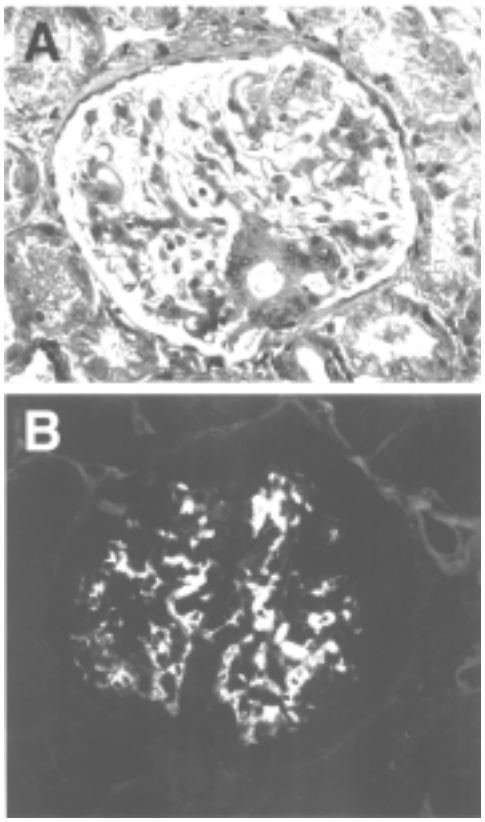

Figure 10. IgA nephropathy. A: mesangial enlargement and hypercellularity (400x). B: coarse and confluent mesangial deposits of IgA (immunofluorescence, 500x).

Pathogenesis

Many aspects of the pathogenesis of IgAN are still unclear. A number of factors that might be involved have been identified, but the data are often conflicting or uncertain. Several abnormalities have been described, not only in the kidneys, but also in the circulation and in other organs.

The findings of immunohistology and of electron microscopy support the hypothesis of an immune-complex disease. Furthermore, the frequent recurrence of the disease in transplanted kidneys and the finding of IgA1 in the glomeruli together with increased amounts of circulating IgA1 and IgA1-containing immune complexes suggest that the immune complexes derive from the circulation.

Although it is not yet established whether there is a reduced clearance of circulating

IgA1 and IgA1-containing immune complexes, it is accepted that there is a an overproduction of IgA1, which is likely to occur in the bone marrow [72]. It is also possible that some abnormalities in the IgA1 molecules may play a pathogenetic role. These might have an abnormal reactivity against specific exogenous or endogenous antigens. Moreover, the deposition of IgA in the mesangium might be favored by a more negative electric charge or by an abnormal *O*-linked glycosylation of the IgA1 [4]. On the other hand, the mesangial cells can have an active role in producing the glomerular and interstitial damage because they can synthesize a number of inflammatory cytokines in response to IgA deposits.

Several other factors might also be involved in the progression of the disease. For example, the angiotensin-converting enzyme (ACE) DD genotype is associated with renal function deterioration [71]. Also, the presence of myofibroblasts in the interstitium may stimulate progressive fibrosis [68], or the peritubular deposition of the complement complex C5b-9 may recruit and activate a number of inflammatory substances [2].

Clinical Presentation and Course

Some patients present with gross hematuria of variable duration. This presentation is more frequent in children than in adults and varies in different geographical areas, being more frequent in North American and European than in Asian-Pacific countries. In about 50% of cases, gross hematuria occurs 24 – 72 hours after a precipitating factor such as pharyngitis, gastroenteritis, urinary infection, fever or strenuous physical effort. Usually gross hematuria is asymptomatic and is not associated with renal function impairment, hypertension, or edema. In some cases, however, there is loin pain, malaise, or myalgia. Rarely, there is a rapid decline of renal function caused by either extracapillary proliferation [1] or by ATN induced by hematuria itself [98]. Recognizing these 2 conditions is important, because patients with the crescentic form require aggressive immunosuppressive treatment, while patients with ATN have a spontaneous recovery of renal function after clearing of gross hematuria.

Asymptomatic microscopic hematuria, either isolated or associated with proteinuria, is the other most frequent presentation in patients with IgAN. This is often found by chance during screening performed for any reason. Microscopic hematuria can be mild or severe and is mixed or dysmorphic by morphology. It is worth remembering that among glomerular diseases IgAN is the most frequent cause of isolated microscopic hematuria [185]. Proteinuria, when present, is mild in the initial phases, < 1 g/day. Exacerbations are possible during infections.

About 5 – 8% of patients present with the nephrotic syndrome. Usually this is associated with renal insufficiency, hypertension, and chronic damage at renal biopsy. However, in rare patients renal function and blood pressure are normal, and at renal biopsy only minor changes are found [182].

Approximately 15 – 20% of patients already have chronic renal insufficiency and hypertension at presentation. However, it is likely that the real prevalence of renal failure caused by IgAN is underestimated due to the reluctance to perform renal biopsies in hypertensive patients with renal insufficiency and hyperechoic kidneys.

IgAN is a chronic disease with variable course. Some patients may do well for many years, while others develop ESRD in short periods of time. The renal survival at 10 years after biopsy varies among different countries, being 67% in North America, 74% in Japan,

81% in Germany, 83% in the United Kingdom, 86% in Australia, and 94% in France [48]. Hypertension, elevated serum creatinine concentration, and increased protein excretion are considered the most important clinical risk factors for renal survival [48]. Among the biopsy finding, glomerular hyalinosis, interstitial fibrosis, and extension of IgA deposits to the peripheral capillary walls are the more reliable indicators of a poor outcome [38].

IgAN can recur after transplantation and, in contrast with a previous view, recurrence is now considered a cause of late graft loss in a considerable number of cases [96, 136].

Diagnosis

The diagnosis of IgAN is based on renal biopsy with the typical finding of dominant IgA at immunohistology. The absence of arthralgia, bloody diarrhea, abdominal pain, and purpura rules out HSP. However, one must be aware that in the latter disease the extrarenal symptoms may rarely develop even months after the renal disease. Recurrent bouts of gross hematuria associated with pharyngitis are rather typical of IgAN but can occasionally also occur in patients with thin basement membrane disease. Asymptomatic microscopic hematuria and proteinuria may suggest a diagnosis of IgAN, but most other glomerular diseases can have a similar presentation. Increased levels of serum IgA, which belong to IgA1 subclass, are observed in 30 – 50% of patients. Usually the serum levels of IgA, either normal or increased, are stable over time. Circulating immune complexes, IgA RF, or circulating levels of some C3 fragments may be found in some cases, but their measurement is more important for research than for clinical practice.

Treatment

The observation that IgAN can lead to renal failure has stimulated a large number of therapeutic trials based on many different approaches, including gluten-free diet, tonsillectomy, phenytoin to reduce serum IgA levels, danazol to dissolve immune complexes, sodium chromoglycate to reduce the mucosal permeability to antigens, antiplatelet/anticoagulant agents and others [108]. These treatments may obtain some reduction of hematuria, serum IgA levels, and/or circulating immune complexes, but there is no clear evidence that any of these treatments could interfere with the progression of the disease.

Uncontrolled trials conducted in small groups of patients showed that glucocorticoids given daily or on alternate days for > 1 year stabilized renal function and reduced proteinuria both in children [193] and in adults [99], with few major side effects. A retrospective study reported that long-term azathioprine at the dose of 2 mg/kg/day together with small amounts of prednisolone preserved renal function [67]. Severe side effects were observed in 3% of patients. Unfortunately, no controlled studies with either glucocorticoids or azathioprine are yet available.

Fish oil, which limits the production or action of eicosanoids and cytokines released during inflammation, has been given with contrasting results in recent controlled studies. Bennet et al. and Petterson et al. did not obtain positive results [11, 142]. However, in a recent, large, multicenter, controlled trial, 12 g/day of fish oil were given for 2 years to IgAN patients with a proteinuria of ≥ 1 g/day or with an increase in serum creatinine of ≥ 25% in the 6 months preceding entry into the study [47]. At an average follow-up of 3 years, renal function was significantly better in the 55 treated patients than in the 56 patients of the placebo group. Compliance to

fish oil was high and side effects minimal. It is possible that the difference with the negative results of the previous controlled trials is due to the higher dosage of fish oil and to the more prolonged treatment used by Donadio et al. It is worth remembering that with this approach the treatment cost is higher.

Several papers showed that ACE inhibitors have a protective effect on renal function and can frequently, but not always, reduce proteinuria [74, 117]. Fosinopril 20 mg once daily or placebo were randomly administered in 4-month sequences to adult patients with normal renal function and normal blood pressure but persistent proteinuria of > 1 g/24 hours [118]. At the end of the period with fosinopril, there was a significant decrease of mean blood pressure, proteinuria, and fractional clearance of albumin and IgG, but there was no effect on creatinine clearance. Recent studies have shown that the response to treatment with ACE inhibitors may be influenced by ACE polymorphism [201].

Considering the available knowledge, we feel that treatment should be limited to the cases at risk of renal failure, namely patients with proteinuria > 1 g/day and/or hypertension. ACE inhibitors are usually well tolerated and can represent the drug of choice in these patients. The results of ongoing controlled studies will be forthcoming. In the meantime, a 6- or 12-month trial with glucocorticoids and/or azathioprine may be attempted to reduce the risk of renal insufficiency. We usually give IV methylprednisolone pulses (0.5 – 1 g each) for 3 consecutive days followed by oral prednisone, 0.5 mg/kg every other day, for 2 months. This course is repeated 3 times for a cumulative treatment of 6 months. Clearly, careful monitoring of side effects is mandatory so that a treatment with still unproven efficacy can be stopped, if necessary.

For 2 subgroups of patients with IgAN, there is a sound indication for treatment. Patients with nephrotic syndrome and minimal change disease at biopsy usually respond well to glucocorticoids, in spite of frequent relapses that remain steroid-sensitive [182]. Patients with rapid decline of renal function due to extensive extracapillary proliferation have a high risk of a poor outcome in the short-term. In these cases, therapy must be aggressive and based on IV methylprednisolone pulses and cytotoxic agents [108]. However, one must be aware that even with this approach the evolution can be unfavorable.

Poststreptococcal Glomerulonephritis (PSGN)

PSGN is characterized by the abrupt onset of hematuria and proteinuria, often in association with edema, hypertension, and mild/moderate renal insufficiency. The disease usually develops several days after a pharyngeal or cutaneous infection caused by group A beta-hemolytic streptococci. The prognosis of PSGN is usually good in the short and long term, but some patients have excessive salt and water retention, and others may slowly progress to renal failure.

Etiology and Epidemiology

PSGN is associated with infections caused by a limited number of strains of group A beta-hemolytic streptococci. These nephritogenic streptococci may be identified by serotyping of a cell wall antigen called M protein. In most cases, streptococcal infection occurs in the upper respiratory tract or in the skin.

Less commonly, PSGN may be preceded by otitis or endocarditis, and may be triggered by other streptococci such as *Streptococcus viridans, Streptococcus mitis* or *Streptococcus mutans*. It must be remembered that in several cases acute GN is not caused by streptococci but is associated with a bacteremic state or with viral or parasitic diseases.

PSGN is the most common primary GN in developing countries, while in the Western world it has become an uncommon disease [166, 175], suggesting that it is favored by low socioeconomic status and poor hygienic conditions. This is also confirmed by the cases occurring in clusters and epidemics, which at times may be even cyclic.

All ages can be affected by PSGN. However, most patients are between 2 and 12 years old. PGN is twice as common in males as in females.

Pathology

In the early phases, there is diffuse mesangial and endothelial cell proliferation, associated with infiltration of the capillary lumens by polymorphonuclear leukocytes and mononucleated cells (Figure 11A). Extracapillary proliferation may involve a few glomeruli, while diffuse and extensive circumferential crescent formation is uncommon, although possible. Cells expressing interleukin-8 (IL-8) and transforming growth factor-beta (TGF-β) [125], as well as cells with increased expression of intercellular adhesion molecule-1 (ICAM-1) can be found both in glomeruli and interstitium [156]. IL-8 correlates with glomerular neutrophil infiltration, while TGF-β correlates with mesangial matrix expansion. The tubulointerstitial compartment is usually normal, but in the most proliferative forms acute cellular infiltrates can be seen.

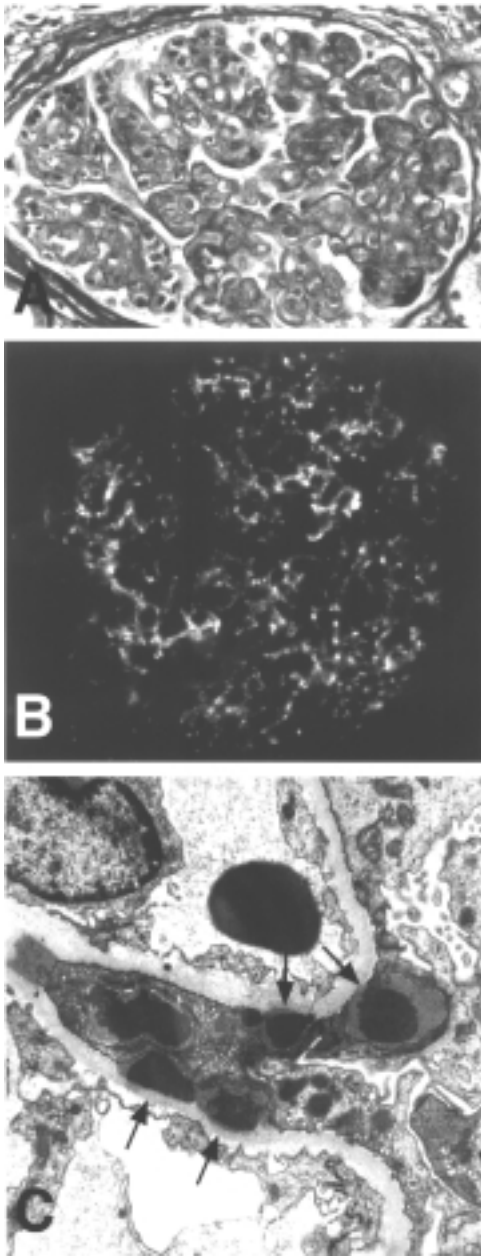

Figure 11. Poststreptococcal glomerulonephritis. A: typical endocapillary proliferation and lobular appearance (400x). B: typical "starry sky" pattern of C3 by immunofluorescence (500x). C: several "humps" (arrows) in subepithelial location (electron microscopy, 7,000x).

The typical immunohistologic pattern is characterized by abundant and well-defined granular deposits of C3 along the outer aspects of the glomerular capillary walls. These deposits confer the appearance known as "starry sky" (Figure 11B). IgG and IgM are present in 60 – 70% of cases. C1q and C4 are generally lacking. Fibrinogen is seen only in crescents.

By electron microscopy, coarse electron-dense subepithelial deposits are the distinguishing feature of PSGN. Due to their shape, the deposits are defined as humps (Figure 11C). However, intramembranous and subendothelial deposits, as well as mesangial deposits, can also be found.

In later phases of the disease, endocapillary proliferation and polymorphonuclear infiltration are less evident, and prominent mesangial deposits can be observed [179]. In other cases, subepithelial deposits are confluent, so that the humps are replaced by apparently elongated deposits, which confer a garland-like pattern at immunohistology [178]. In cases without complete resolution, the typical endocapillary disease can transform, over time, into a mesangiocapillary pattern.

Pathogenesis

Some data suggest that PSGN is an immune-complex disease, in which some components of nephritogenic streptococci are likely to act as antigens. Cell membrane antigens, streptococcal cationic proteinase, extracellular plasmin-binding protein, and endostreptosin or preabsorbing antigen have been proposed as possible triggers for the formation of the immune complexes. On the other hand, anti-immunoglobulin antibodies could be involved in the pathogenesis of PSGN, as demonstrated by the high titers of rheumatoid factor and by the presence of anti-immunoglobulin deposits in the renal biopsy of some patients [159]. An important role in conferring antigenicity to immunoglobulins can be played by another streptococcal component, the neuraminidase. This, in fact, can cause desialization and consequent modifications of autologous immunoglobulins. Moreover, neuraminidase can desialize leukocytes and favor their deposition in the glomeruli and interstitium [116].

Cellular immunity may also be involved in the pathogenesis of PSGN, as suggested by glomerular and interstitial infiltration of granulocytes, monocyte/macrophages, and T lymphocytes [156], increased IL-8 and TGF-β in the kidneys [125], and increased IL-6 and tumor necrosis factor-α (TNF-α) in the circulation [180].

Clinical Presentation and Course

The typical presentation of PSGN is an acute nephritic syndrome, i.e. oliguria, edema, hypertension, and gross hematuria 10 – 21 days after an upper respiratory tract or a skin infection. Nonspecific symptoms such as malaise, weakness, and nausea are frequent. Dull lumbar pain is present in 5 – 10% of patients. Although rare, an extrarenal disease is possible in patients with PSGN, as demonstrated by the association with scleritis or cerebral vasculitis. Decreased GFR and salt and water retention are the main causes of edema and hypertension, as documented by the finding of increased plasma volume and cardiac output in most patients with PSGN. In children, edema is usually generalized, while in adolescents and adults it is more frequently confined to face and legs. Hypertension is observed in > 80% of patients, but in only 50% of cases require treat-

ment. In rare cases, however, hypertension may be severe and cause hypertensive encephalopathy. Especially in elderly patients, oliguria and fluid retention can cause heart failure and death. Proteinuria is common in PSGN; however, nephrotic proteinuria is rare, especially in children.

In other patients, PSGN can be asymptomatic and cause only transient serum complement decrease and/or mild urinary abnormalities such as isolated microscopic hematuria [202], with or without hypertension. Prospective studies in families have shown that this presentation is more frequent than the overt clinical presentation described above [160]. Very rarely, PSGN is not associated with urinary abnormalities in spite of clinical symptoms and the presence of endocapillary glomerulonephritis at biopsy.

Usually the nephritic symptoms spontaneously reverse 4 – 7 days after the onset. However, urinary changes, mild renal function impairment, or hypertension can persist or develop months or years after the acute episode. These abnormalities can be found in approximately 20% of patients 1 – 2 decades after the onset. Usually children do better than adults. Patients with a nephrotic syndrome at presentation and those with extensive deposits in the peripheral capillary loops have a poorer prognosis [190]. Patients with crescentic disease may recover spontaneously. However, the prognosis is poor when crescents involve > 60% of glomeruli [127]. In some patients with subclinical presentation, persistent or intermittent microscopic hematuria may be seen at long-term follow-up [202].

Diagnosis

Several renal and systemic diseases can present with an acute nephritic syndrome: IgA nephropathy (IgAN), mesangiocapillary glomerulonephritis, anti-GBM disease, SLE, cryoglobulinemia, HSP, and systemic microscopic vasculitis. However, the finding of a preceding infection of the upper respiratory tract or of the skin, increased antistreptolysin (ASO) titers, decreased C3 levels, and the lack or rareness of extrarenal symptoms strongly suggest a diagnosis of PSGN.

In PSGN the infection typically precedes the nephritis by 10 – 21 days, while the episodes of gross hematuria in IgA nephropathy usually follow infections by hours or only a few days. In addition, while IgA nephropathy tends to cause repeated episodes of gross hematuria, PSGN is rarely recurrent.

Increased ASO titers are observed in 40 – 90% of patients with PSGN. This is much less common in other conditions. In PSGN, > 90% of patients have a decrease of C3 and normal C4 serum levels, indicating an activation of the alternative pathway of complement. In most cases C3 returns to normal in < 8 weeks, even though a prolonged decrease of C3 is possible [42]. The behavior of complement distinguishes PSGN from lupus nephritis in which both C3 and C4 are usually reduced in active phases. In type II cryoglobulinemic nephritis, usually only C4 is strongly decreased. In type II MPGN, similar to PSGN, C3 is low while C4 is normal. However, C3 remains persistently low because of the presence of C3 nephritic factor.

Usually there are no extrarenal symptoms in PSGN besides edema and hypertension. This differentiates PSGN from systemic diseases causing acute nephritic syndrome. However, it should be remembered that in occasional patients with PSGN extrarenal symptoms such as scleritis and cerebral vasculitis may be present, and that even a positive ANCA is possible [5].

PSGN can be easily diagnosed in epidemic or family cases, even when there are only

transient and minor clinical and urinary changes. However, for sporadic cases with only persistent urinary abnormalities, distinguising between IgA nephropathy, thin basement membrane disease, or other conditions can be difficult without renal biopsy.

Is renal biopsy indicated for patients with acute nephritic syndrome caused by PSGN? For patients presenting with a typical history and clinical picture, the diagnosis is easy and does not need a confirmatory biopsy. However, renal biopsy may be indicated for patients with atypical history or presentation, and especially for cases with severe or prolonged renal failure, which can be caused by crescentic disease.

Table 12. Classification of Crescentic Glomerulonephritis

Type I: Anti-GBM disease
(linear deposition of IgG along the BM)
Renal disease only
Renal and pulmonary disease (Goodpasture's disease)
Type II: Immune-complex associated disease
(granular immunodeposits in the glomeruli)
Primary glomerular diseases
Secondary glomerular diseases
Type III: Pauci-immune disease
(no or scanty immunodeposits in the glomeruli)
ANCA-associated disease
Idiopathic crescentic glomerulonephritis

Treatment

Patients with oliguria, edema, and hypertension need close observation and care. Restriction of sodium and fluid intake are mandatory. Furosemide or other loop diuretics are frequently needed. In many patients, hypertension reverses with the correction of fluid overload and edema. However, in some patients antihypertensive agents are needed. Antistreptococcal antibiotics such as penicillin, cephalosporins, erythromycin or derivatives should be given to patients with positive throat or skin cultures.

Glucocorticoids or immunosuppressive agents are not indicated in PSGN because of spontaneous resolution of the disease in most cases. However, in patients with extensive crescent formation and slow resolution of symptoms, a short course of high-dose glucocorticoids may be considered.

Crescentic Glomerulonephritis (CGN)

CGN encompasses several diseases with different etiologies and pathogenetic mechanisms that have in common a rapid deterioration of renal function and the presence of crescents in > 50% of glomeruli at renal biopsy. The natural course is usually poor. However, early and vigorous treatment can significantly improve the prognosis of these disorders.

According to the immunopathology findings, the various forms of CGN can be grouped into 3 categories (Table 12).

Type I CGN

The hallmarks of type I CGN, or anti-GBM disease (anti-GBM disease), are the presence of anti-GBM autoantibodies in the circulation

and their linear fixation along GBMs. When these antibodies also fix to the basement membrane of pulmonary alveoli, a pulmonary-renal disorder ensues, which is known as Goodpasture's disease.

Anti-GBM disease accounts for approximately 10% of all CGN [86].

Etiology and Epidemiology

Genetic factors play a role in the etiology of the disease, as demonstrated by several familial cases [176]. Immunogenetic studies have shown a linkage with HLA-DR2 and -DR4 antigens, as well as a negative association with HLA-DR7 and -DR1 [28].

Environmental factors are also important. The disease can appear or recur after infections or exposure to organic solvents, hydrocarbons, or cigarette smoking [94, 200]. The clustering of cases in different geographic areas further supports the role of environmental factors.

Anti-GBM disease can be associated with a number of other disorders including lymphoma, crescentic membranous nephropathy [104], and ANCA-positive vasculitis [19].

Anti-GBM disease is rare, but occurs more commonly in Caucasians than other races. Males are more frequently affected than females. All ages can be involved, the peaks being in the third, sixth, and seventh decades of life. Children are more rarely and less severely affected than adults [63].

Pathology

In the early phases, renal biopsy may show focal or diffuse mesangial proliferative GN. In the most typical cases, there are extensive crescents and necrosis of the glomerular tufts (Figure 12). Crescent formation is initiated by

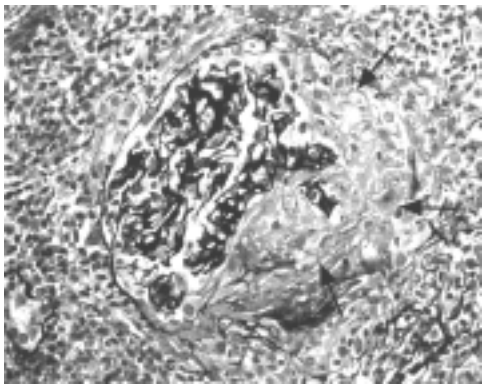

Figure 12. Extracapillary glomerulonephritis with a large fibro-cellular crescent (arrows) occupying the Bowmans space (400x).

holes in the GBM, caused by the antibody attack [17]. Leakage of intravascular content into Bowman's space follows, with consequent fibrin generation and cell recruitment. Several types of cells are found in crescents including visceral and epithelial cells, monocytes, and T lymphocytes [20]. Collagen is then produced, either by the cells forming the crescents of by fibroblasts invading the Bowman's space from ruptured Bowman's capsules [181]. This is followed by fibrotic transformation of the crescents and permanent glomerular damage.

Interstitial inflammation is frequent. Its severity is correlated with the extent of antibody fixation to the tubular basement membranes of the distal tubules. Vasculitis of the kidney is also possible [199].

By immunohistology, linear staining of IgG along the basement membrane of glomeruli (Figure 13), distal convoluted tubules, and collecting ducts is a typical and constant feature of anti-GBM disease. In 60 – 70% of cases, linear deposits of C3 can also be seen.

By electron microscopy, irregularities and breaks of the GBM are the most typical findings.

In the lungs there is often intra-alveolar hemorrhage associated with thickening,

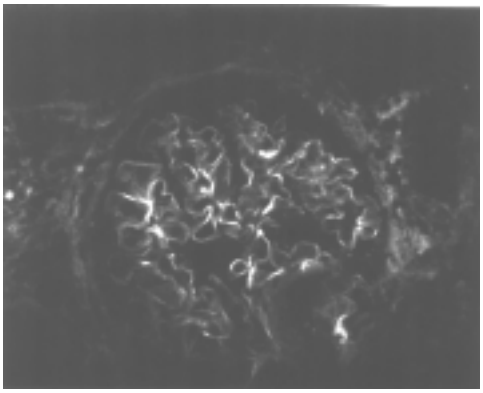

Figure 13. Anti-glomerular basement membrane disease. Linear IgG along the GBM (immunofluorescence, 500x).

edema, and fibrosis of the alveolar membrane. In addition, there are siderin-containing macrophages, deposits of fibrin, and leukocyte infiltration. By immunohistology, there is a typical linear fixation of IgG along the alveolar basement membranes with a patchy distribution.

Pathogenesis

Anti-GBM disease is due to the production of autoantibodies directed against the so-called Goodpasture antigen. The autoantibodies belong to IgG1 and IgG4 subclasses of IgG. However, autoantibodies of IgA class may rarely be found in both the circulation and in tissues [163]. Goodpasture antigen is located on the 230 amino-acid, carboxyterminal, noncollagenous domain of the α-3 chain of type IV collagen, which is one of the main components of the basement membrane [189].

As in other antibody-mediated conditions, there is activation of cell-mediated immunity. T-lymphocytes of patients with anti-GBM disease proliferate when exposed to purified or recombinant Goodpasture antigen [43], and there are a number of T-lymphocytes among the cells infiltrating the kidney [135].

Clinical Presentation and Course

Two-thirds of patients with anti-GBM disease have both renal and lung disease at presentation, while one-third apparently have only renal disease. Lung disease is more common in younger patients and in men. Renal disease is more common in older patients and in women [188].

Malaise, mild arthralgia, and mild weight loss can precede the renal and lung manifestations. These symptoms can be more severe in patients with associated vasculitis and positivity for ANCA. However, some ANCA-positive patients do not have systemic symptoms.

In sporadic cases the renal disease may be mild, causing only minor urinary abnormalities such as isolated microscopic hematuria. Occasionally there may be a history suggesting a subacute or chronic GN. However, in most cases the renal disease is severe and rapidly progressive, so that many patients present with renal failure associated with a nephritic urinary sediment and/or oliguria. Gross hematuria is also common. Proteinuria is constant but is rarely in the nephrotic range. Hypertension is uncommon.

Hemoptysis, trivial or severe, is the most typical sign of lung disease. However, there may be patients without hemoptysis who have life-threatening alveolar bleeding. This can cause microcytic anemia, which is frequent in patients with anti-GBM disease.

If treated promptly and vigorously, anti-GBM disease can subside without recurrences, but in some patients the disease may lead to irreversible renal lesions. Usually lung disease resolves without persistent damage. In other cases, the course may be marked by

remission and recurrences of either renal or lung disease or both, months to years after the first manifestation. Recurrences may be favored by infections or exposure to organic solvents. The reappearance of circulating anti-GBM antibodies without clinical symptoms is also possible [76].

After renal transplantation, anti-GBM antibodies can deposit on transplanted kidneys but frequently without clinical consequences. To reduce the probability of recurrence, transplantation should be postponed until 6 months or more after the disappearance of circulating antibodies. Rarely, an anti-GBM crescentic GN without lung involvement may develop in renal transplant recipients with Alport syndrome [137]. Patients with Alport's syndrome are unable to synthesize α-5 chains of type IV collagen, due to a mutation in the gene COL4A5 on the X chromosome. After renal transplantation, the α chains are recognized as foreign antigen by the recipient immune system, with consequent production of anti-GBM antibodies and development of renal disease [92].

Diagnosis

The presence of a rapidly progressive renal disease with active urinary sediment, hemoptysis, and sideropenic anemia should always raise the suspicion of an anti-GBM disease. Circulating IgG antibodies are the clue for differential diagnosis with other diseases that an also cause a similar clinical picture, such as SLE, HSP, cryoglobulinemia, and pauciimmune systemic vasculitis. Radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) are sensitive and specific methods to detect and titer these antibodies. While antibody titers correlate with the severity of renal damage [75], no correlation has been found with the severity of lung disease.

ANCA can be positive in a number of patients with anti-GBM disease [19]. In most cases, positivity is perinuclear by indirect immunofluorescence (p-ANCA). However, cytoplasmic positivity (c-ANCA) is also possible. As in systemic vasculitis, ANCA titers can be used to monitor the activity of the disease [85]. Because of their possible association, ANCA and anti-GBM antibodies should always be sought in either disorder.

Chest X-rays show symmetrical or asymmetrical lesions of variable size, which can clear 48 hours after bleeding. Increase of carbon monoxide uptake by the lungs, caused by the presence of free hemoglobin in the alveoli, is typical of Goodpasture's disease [53]. The patchy distribution of linear IgG in the pulmonary alveoli makes the diagnosis of anti-GBM disease by transbronchial biopsy unreliable [89].

Treatment

In the last 3 decades, patient and renal survival has dramatically improved. The 1-year mortality rate decreased from 96% in 1964 [12] to 7% to 11% in the 1990s [75, 122], and renal survival increased from 4% to about 40%. Improvement of supportive therapies, such as dialysis and artificial ventilation, and a more refined specific treatment have both contributed to the improved prognosis.

The aim of therapy should be to remove circulating antibodies, prevent the formation of new antibodies, and reduce the inflammatory consequences of antibody deposition on basement membranes. Today, the specific treatment of anti-GBM disease is based on plasma exchange associated with immunosuppressive agents [188]. A suggested schedule for patients with lung and renal disease includes oral prednisolone 1 mg/kg/day, oral cyclophosphamide 3 mg/kg/day, and daily

plasma exchange for 14 days or until the circulating antibodies are suppressed. High-dose IV methylprednisolone pulses can also be used at the beginning of therapy in patients with rapidly a progressive course, but when given alone they are of little efficacy. With such an approach, pulmonary hemorrhage is generally arrested in 24 – 48 hours, and substantial improvement of renal function is usually achieved. However, for patients who present with oliguria and/or a serum creatinine of > 6.8 mg/dL (600 μM) and/or a high percentage of crescents at biopsy, renal survival is still poor despite aggressive therapy [75, 89]. The duration of treatment should be decided on the basis of the clinical data and of circulating antibody titer. After remission, prednisone can be progressively reduced, and therapy may be withdrawn in about 3 months [188]. If severe renal or pulmonary disease recurs, the full treatment should be reinstituted. However, the risk of potentially life-threatening infections favored by immunosuppression must always be kept in mind.

Type II CGN

Type II CGN accounts for approximately 30% of cases of CGN [86]. This type includes a heterogeneous group of renal diseases characterized by glomerular deposits of immunoglobulins and/or complement at immunohistology (Table 13).

Etiology

The majority of the disorders causing type II CGN belong to primary or secondary proliferative glomerular diseases. However, non-proliferative forms, such as membranous nephropathy (MN) [104] and amyloidosis [128], can sometimes be complicated by severe extracapillary proliferation.

Table 13. Main Immune Complex Glomerular Diseases that can be Associated with Extensive Extracapillary Proliferation

Primary Glomerular Diseases
Acute post infectious glomerulonephritis
IgA nephropathy
Mesangiocapillary glomerulonephritis
Membranous nephropathy
Secondary Glomerular Diseases
Lupus nephritis (especially class IV)
Henoch-Schönlein purpura nephritis
Cryoglobulinemia
Amyloidosis
Light chain deposition disease
Glomerular diseases associated with malignancies

Pathology

As a general rule, type II CGN shows fewer necrotizing glomerular lesions on light microscopy than type I and type III CGN. On the other hand, immune complex-mediated CGN has more prominent intracapillary proliferation, mesangial expansion, and thickening of the glomerular capillaries.

Clinical Presentation and Course

The clinical presentation is characterized by rapidly progressive renal failure associated with active urinary sediment, possible oliguria or gross hematuria, and hypertension. In secondary renal diseases, the development of a crescentic form can be associated with an exacerbation of the extrarenal symptoms and/or an abrupt increase of serological markers.

The outcome of untreated forms is usually poor. As in type III CGN, reversal of renal failure and other symptoms can be achieved by early treatment based on high-dose corticosteroids and immunosuppressive drugs (see type III CGN).

More information about the forms belonging to this group is found in Volume 1 Chapter I.8.

Type III CGN

Type III CGN accounts for about 60% of all cases of CGN [86], and includes renal diseases with scanty or absent immune deposits at immunohistology or on electron microscopy.

Etiology

Some patients only have renal symptoms while others have features suggesting a systemic disorder. More than 80% of patients with type III CGN are ANCA-positive, especially p-ANCA [153]. In addition, most patients with type III CGN, even those without extrarenal symptoms, have small vessel vasculitis, such as microscopic polyarteritis, Wegener's granulomatosis, Churg-Strauss syndrome, or other more rare forms.

It is not clear whether the minority of patients without any clinical or laboratory signs of vasculitis actually have an idiopathic CGN or are affected by a vasculitis with negative serological markers and only renal disease [65].

Pathology

By light microscopy, there is extracapillary glomerulonephritis often associated with segmental fibrinoid necrosis of the glomerular tuft. At immunohistology there are no immune deposits. In some cases, scanty granules of immunoglobulin or complement can be seen. No specific findings are observed by electron microscopy.

Clinical Presentation and Course

At presentation, most patients have constitutional symptoms that include fever, weight loss, and malaise. Renal function is variably impaired, with or without reduced urine output. Urinalysis indicates nephritic urinary sediment and variable proteinuria. Normochromic anemia, leukocytosis, and thrombocytosis are common.

Treatment

Irrespective of the presence of systemic symptoms and ANCA antibodies, type III CGN deserves early treatment.

The treatment of type III and type II CGN is based on the association of high-dose IV methylprednisolone pulses with immunosuppressive agents, while the role of plasma exchange is less established.

Even though no controlled therapeutic trials are available, methylprednisolone pulses represent the mainstay therapy for type III CGN. About 75% of patients with type III and almost 90% of patients with type II CGN can obtain improvement of renal function with IV methylprednisolone pulses [16]. The response is usually rapid, and failure to respond within 2 weeks can be considered as a sign of advanced nonresponsive disease [65]. Methylprednisolone pulses are usually well tolerated, even though transient side effects such as tremor, flushing, dysgeusia, epigastric pain, seizures, hyperglycemia, renal function

impairment, cardiac arrhythmias, or hypercoagulability can occur [143]. Usually a course includes 3 – 5 IV pulses of methylprednisolone of 0.5 – 1 g each given daily or every other day. Repeated courses can be given to relapsing patients. After an IV pulse course, oral prednisone is started at a dose of 0.5 – 1 mg/kg/day. Tapering of the dosage is also empirical, being modulated on the evaluation of the general clinical conditions and the severity of the disease.

Glucocorticoids are usually combined with cyclophosphamide, which proved to be efficacious in patients with vasculitis [78]. The drug is preferably given orally at a dosage of 2 – 3 mg/kg/day, which should be halved in patients with renal failure to reduce side effects. In CGN the IV route (500 – 1000 mg/m^2 every month or every 3 months) is usually limited to patients who do not tolerate oral administration. As for oral prednisone, the duration of treatment is based on the evaluation of the clinical situation. Some physicians prefer to switch from cyclophosphamide to azathioprine after 3 months to reduce the risk of myelotoxicity, hemorrhagic cystitis, and neoplasia. Others prefer to give cyclophosphamide for more prolonged periods of time to maximize the chances of renal function recovery [65].

While plasma exchange has a key role in the treatment of anti-GBM disease, its role in type II and type III CGN is still debated. In 2 randomized trials comparing plasma exchange plus immunosuppressive agents vs. immunosuppressive agents alone in non-anti-GBM disease patients, no difference could be seen between the 2 treatments [35, 66]. A third controlled study has reported that the addition of plasma exchange to immunosuppressive agents can more frequently obtain a partial recovery of renal function in dialysis-dependent patients [154]. However, even in the latter trial the beneficial effects of plasma exchange were short lived, because most patients in whom renal function improved had to start dialysis or died at further follow-up. Thus, it seems reasonable to limit plasma exchange to severely ill patients who have not responded to more conventional treatment.

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Diabetic Nephropathy

Julia Breyer Lewis

Key Points

Both alterations in systemic and glomerular hemodynamics and changes in metabolism due to hyperglycemia are crucial factors in the pathogenesis of diabetic nephropathy.

Microalbuminuria and proteinuria are key markers which identify patients with diabetes mellitus (DM) who have developed diabetic nephropathy. Intensive glycemic control dramatically reduces the risk of developing diabetic nephropathy.

Blood pressure control slows the progression of diabetic nephropathy even after deterioration of renal function starts. Angiotensin-converting enzyme (ACE) inhibition slows the progression of diabetic nephropathy and is indicated for all normotensive or hypertensive diabetic patients who have microalbuminuria or proteinuria.

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States leading to enrollment in the Medicare ESRD program. Patients with DM currently account for 35% of the population requiring renal replacement therapy. Patients with Type II diabetes mellitus (DM) constitute 60% of the diabetic population in the ESRD program. The cost to Medicare for these patients' renal replacement therapy alone exceeds 2 billion dollars per year [1]. In addition to its significant impact on health care costs, diabetic kidney disease significantly shortens the lifespan of the patient with diabetes. It has been estimated that patients with Type I DM and nephropathy (manifested by proteinuria) have a 100-fold greater risk of death relative to a nondiabetic population. Patients with DM without kidney disease have only a 2-fold increase in relative mortality [2].

Epidemiology

The cumulative incidence of nephropathy in patients with Type I DM of 40 years duration is 40%. Several reports suggest that the cumulative incidence of diabetic nephropathy is declining, which may reflect better blood sugar control in the diabetic population as a whole. The annual incidence peaks just before 20 years duration of DM and declines thereafter (Figure 1) [2]. The decline in the annual incidence of diabetic nephropathy over time

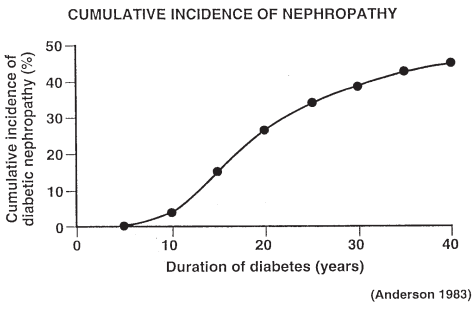

Figure 1. Cumulative incidence of diabetic nephropathy in relation to duration of diabetes in 907 Type I patients.

suggests that the pool of susceptible patients becomes exhausted. Diabetic nephropathy with proteinuria rarely develops before 10 years duration of DM or after 30 years of DM. Thus, the development of diabetic nephropathy is not simply a function of duration of DM nor an inevitable complication in all patients. Rather, the data suggest that only a subset of 40% of patients with Type I DM develop diabetic nephropathy, perhaps because of a genetic susceptibility or an environmental exposure.

Reports of familial clustering of diabetic nephropathy are consistent with a genetic susceptibility to the development of this complication. In families with multiple siblings who have Type I DM, those of a proband with diabetic nephropathy are more likely to have proteinuria and renal insufficiency secondary to diabetic nephropathy than the siblings of duration-matched pro-bands without nephropathy. Similar data supporting genetic susceptibility to diabetic nephropathy have also been reported in families with Type II DM.

Early studies suggested that the cumulative incidence of diabetic nephropathy in patients with Type II DM was less than in patients with Type I DM. However, a recent careful natural history study done in Pima Indians with Type II DM reported a cumulative incidence of diabetic nephropathy comparable to that found in Type I DM patients [3]. Furthermore, in Western Europe it has been reported that up to 40% of patients with Type II DM developed nephropathy, a cumulative incidence quite similar to that found in Type I DM [4]. In part, some of the discrepancies between these reports may reflect the very high mortality rate from atherosclerotic disease in patients with Type II DM and renal disease, resulting in a bias against the progression to ESRD.

For most Type II patients, the age of onset of DM is unknown and may precede the diagnosis by many years. Some patients with Type II DM already have diabetic nephropathy at the time of diagnosis of DM. However, in the Pima Indian study, the age of onset of DM is well documented and precedes proteinuria from diabetic nephropathy by approximately 20 years. Assuming that the natural history of diabetic nephropathy in Pima Indians is representative of all patients with Type II DM, the duration of DM required to develop nephropathy may be similar for Type I and Type II DM.

Finally, there are important racial differences that contribute to the risk of developing diabetic nephropathy. African Americans, Mexican Americans, American Indians, Maori, and Polynesians with DM have a greater risk of developing diabetic nephropathy and a more rapid progression to ESRD than Caucasians [3]. It is not known whether these racial differences are the result of genetic, environmental, or other factors.

Pathogenesis and Risk Factors

Many factors have been postulated to be important in the pathogenesis of diabetic nephropathy. It appears that exposure to both the systemic hemodynamic effects of DM and to the diabetic milieu are critical factors for the development of diabetic kidney disease. In studies with diabetic rats and humans, unilateral renal artery stenosis has been reported to protect the kidney distal to the blocked renal artery from developing the morphologic changes of DM. Thus, exposure to the systemic blood pressure appears to contribute to the development of diabetic kidney disease.

Normal kidneys transplanted into patients with DM develop diabetic lesions over time,

whereas kidneys inadvertently harvested from patients with DM transplanted into non-diabetic ESRD patients showed resolution of their diabetic lesions on microscopy. This suggests that exposure to the diabetic milieu, rather than an intrinsic defect in the kidneys predisposes these patients to the development of diabetic nephropathy.

Hyperglycemia, insulin insufficiency, augmented glucagon and growth hormone levels, and increased ketogenesis have all been implicated in the pathogenesis of diabetic nephropathy. More recently, it has been demonstrated that hyperglycemia results in the glycosylation of long-lived proteins that crosslink to form advanced glycosylation end products (AGEs) [5]. In animal models, the accumulation of AGEs is associated with the end-organ complications of DM. Similarly, in humans the accumulation of AGEs is increased in patients with renal insufficiency. Inhibitors of AGE formation are beneficial in retarding the progression of diabetic nephropathy in experimental animals and are currently being tested in human clinical trials.

Hyperglycemia also leads to the shunting of glucose down the polyol pathway with the accumulation of sorbitol in the lens, nerves, and kidney. In animal models, this pathway has been implicated in the development of diabetic nephropathy, but it is unclear what role it may play in human diabetic kidney disease [6].

Alterations in the renin-angiotensin system also contribute to the development of diabetic nephropathy in animal and human models, as do abnormal intraglomerular pressures in animal models. In the diabetic rat, decreasing intraglomerular pressures by decreasing angiotensin (Ang) II-mediated efferent arteriole resistance preserves glomerular structure and function [7]. Similarly, in humans, interrupting the renin-angiotensin system (see below) slows the progression of diabetic kidney disease. Together, these studies imply that alterations in the renin-angiotensin system play an important role in the pathogenesis of diabetic nephropathy. Additional important factors in this process may be alternations in the production of prostaglandins or kinins.

Identifying the risk factors for development of diabetic nephropathy in humans may help identify important pathogenic mechanisms in the development of this disease [8]. Significant risk factors include a family history of diabetic nephropathy, the presence of hypertension, poor glycemic control, smoking, and increased plasma pro-renin activity. In large population studies, patients with DM have significantly elevated blood pressures compared with non-diabetic controls. The presence of proteinuria in these patients is predictive of the presence of hypertension. Some, but not all, studies suggest that at the time of diagnosis of DM, patients destined to develop diabetic nephropathy have significantly higher mean arterial blood pressures than those patients with DM who never develop nephropathy. Furthermore, patients with both Type I and Type II DM and nephropathy have a predisposition to hypertension, as indicated by elevated sodium-lithium counter transport activity in erythrocytes and a strong parental history of hypertension as compared to diabetic patients without nephropathy. Combined, these data make a compelling arguement that a genetic predisposition to hypertension is a risk factor for developing diabetic nephropathy. However, since it has been reported that up to 25% of patients with Type I DM and established diabetic nephropathy are normotensive, a genetic susceptibility to hypertension cannot be the only risk factor in the development of diabetic nephropathy.

Hyperglycemia is clearly necessary for the development of diabetic nephropathy in animals and humans. Many retrospective clinical studies have documented a relationship be-

tween poor blood sugar control and the subsequent development of diabetic nephropathy. Patients with poor blood sugar control develop diabetic nephropathy earlier. Poor glycemic control also synergistically increases the risk for diabetic nephropathy in patients genetically predisposed to hypertension.

Smoking is a risk factor identified in multiple epidemiological studies for the development and more rapid progression of diabetic nephropathy. The mechanism for the effects of smoking on kidney disease is unclear. Increased plasma pro-renin activity has also been associated with an increased risk of patients developing diabetic retinopathy and nephropathy, although there is considerable overlap in the plasma pro-renin activity between patients with and without complications.

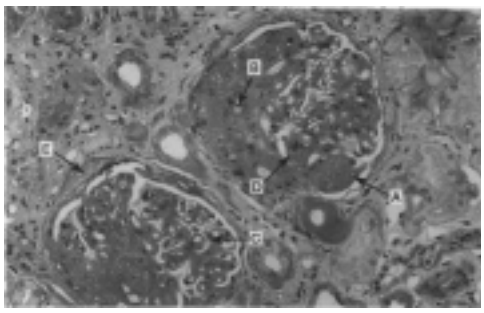

Figure 2. Five distinctive lesions in glomeruli of patients with insulin-dependent diabetes mellitus. A = Kimmelstiel-Wilson nodule; B = intercapillary glomerulosclerosis;C = thickening of glomerular basement membrane; D = mesangial expansion; E = fibrin cap lesion.

Pathology

Renal biopsies are normal in patients at the time of diagnosis of Type I DM. Within as little as 1 – 2 years, however, morphologic changes appear, including glomerular basement membrane thickening, mesangial expansion, nodular and diffuse forms of intracapillary glomerulosclerosis, the capsular drop lesion, and the fibrin cap and arteriolar hyalinosis (Figure 2). Glomerular basement membrane thickening is a sensitive indicator for the presence of DM, but does not predict which patients will develop clinically significant nephropathy. In contrast, mesangial expansion has been demonstrated to correlate with clinically significant diabetic nephropathy [9]. Glomerular filtration rate (GFR), as measured by creatinine clearance, declines linearly with the degree of mesangial expansion. Although DM is primarily a vascular (including glomerular) disease, alterations in the structure and function of the renal tubulointerstitium are also present. The degree of interstitial fibrosis also correlates with the reduction in GFR. Many patients will have morphologic changes in the kidney consistent with the effects of DM but never develop proteinuria or other clinical manifestations of diabetic nephropathy.

The morphologic changes found in patients with Type II DM and diabetic nephropathy were long thought to be indistinguishable from those in patients with Type I DM. Careful prospective biopsy studies have demonstrated that patients with Type I and Type II DM share the nodular form of intracapillary glomerulosclerosis (Kimmelstiel-Wilson-lesions). However, patients with Type II DM have more prominent non-nodular glomerulosclerosis, arteriolar hyalinosis, and other vascular changes.

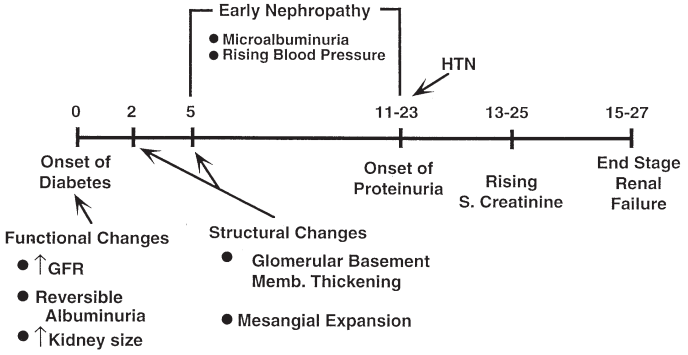

Figure 3. The natural history of diabetic nephropathy.

Natural History

The natural history of diabetic nephropathy is best understood in patients with Type I DM and is illustrated in Figure 3.

At the time of diagnosis of Type I DM, functional changes in the kidney are manifested in virtually all patients [7]. Within a few years, morphologic changes occur in the kidneys of most patients. Glomerular hyperfiltration, elevations in the systemic mean arterial blood pressure, and poor blood sugar control all appear to be important features in this early period. Nephropathy is manifested early by microalbuminuria, with the majority of patients progressing to overt proteinuria. On average, proteinuria is present in the 40% of patients who were destined to develop diabetic nephropathy 10 – 25 years after the onset of Type I DM. Once proteinuria is established, renal function declines inexorably, with 50% of patients reaching ESRD within 7 – 10 years.

Patients with Type II DM frequently have an unknown age of onset of DM and many co-existing illnesses complicating their course. For example, Type II diabetics have a high cardiovascular mortality and often do not survive long enough to develop ESRD from diabetic nephropathy. However, as noted above, studies of the Pima Indians indicate analogous progression in Type II DM compared to Type I [3, 4].

Functional Changes

At the onset of DM, kidney size is increased and albuminuria is present, but these changes usually reverse with blood sugar control. The iniation of insulin therapy also lowers the dramatically increased GFR, although it remains supranormal compared to a nondiabetic population. In both retrospective and prospective studies, higher GFRs at the time of diagnosis of DM predicted the later development of diabetic nephropathy [10]. A GFR of 125 mL/min or less had a negative predictive value of 95% in Type I patients, while a GFR > 125 mL/min had a 53% positive predictive value for the development of nephropathy. However, because of overlap in these patient populations, an early measurement of GFR alone cannot solely predict diabetic renal disease. In patients with Type II DM, reports vary widely about the presence or absence of glomerular hyperfiltration. This may reflect the difficulty in establishing the length of DM in these patients. In the Pima Indians, early glomerular hyperfiltration similar to that reported in patients with Type I DM has been documented.

In animal models of DM, glomerular hyperfiltration is associated with increments in renal flow because of renal dilatation and increases in the glomerular transcapillary hydraulic pressure gradient. These changes lead to accelerated glomerulosclerosis. It is likely that similar glomerular damage associated with glomerular hyperfiltration occurs in humans. Glomerular hyperfiltration has also been associated with increased glomerular surface area and renal hypertrophy.

Microalbuminuria

The presence of microalbuminuria (albumin excretion of 30 – 300 mg/24 hour) in patients with DM is highly predictive of the progression to proteinuria and renal insufficiency in the next 10 – 15 years. The reported prevalence of microalbuminuria in patients with Type I DM varies widely, depending, at least in part, on how the population is selected in terms of DM duration. Overall, approximately 20% of patients with Type I DM will have microalbuminuria in cross-sectional studies. Poor glycemic control and elevations in mean arterial blood pressures also correlate with the development of microalbuminuria [11]. Once present, microalbuminuria is highly predictive of progression to overt proteinuria and renal insufficiency. Between 75% and 100% of patients with documented microalbuminuria go on to proteinuria and declining renal function. The GFR in patients with microalbuminuria is well preserved or increased, but may begin to decrease once the urinary albumin excretion rate exceeds 100 μg/min. Type II patients also develop microalbuminuria, which also predicts progression to proteinuria and ESRD. However, microalbuminuria is associated with a high mortality rate due to atherosclerotic events in these patients, many of whom do not survive to develop proteinuria or ESRD.

Proteinuria and Declining Renal Function

For the vast majority of patients with diabetic nephropathy, proteinuria inevitably progresses to renal decline. In patients with either Type I or Type II DM, the proteinuria typically ranges from 0.5 gm to more than 20 gm/24 hour. In early nephropathy, albuminuria is secondary to a loss of the anionic charge barrier, whereas in established nephropathy, proteinuria results from an increased number of nonselective enlarged pores. Proteinuria typically occurs 17 years (± 6 years) after the onset of Type I DM.

Once proteinuria is established, GFR begins to decline, with an average reported rate of loss between 3 – 12 mL/min/yr. The decline in renal function can be hastened by other diabetic complications such as neurogenic bladder, urinary tract infections, papillary necrosis, and exposure to renal toxins such as IV contrast. Other factors that predict a faster progression include uncontrolled systemic hypertension, uncontrolled blood sugars, higher protein excretion rates, hypercholesterolemia, smoking, and a parental history of DM. Certain racial groups, such as African Americans, Mexican Americans, Native Americans, Polynesians, and Maori, all have a faster rate of progression to ESRD than Caucasians with diabetic nephropathy [4].

End-stage Renal Disease (ESRD)

Once patients with DM reach ESRD, their options include hemodialysis, peritoneal dialysis, or transplantation. ESRD patients with DM have higher mortality rates than nondiabetic ESRD patients. Peritoneal dialysis avoids the problems associated with hemodialysis, such as vascular access, hemodynamic instability, and systemic heparin, but is complicated by increased glucose loads, worsening triglyceride levels, and peritonitis. Hemodialysis provides higher small molecular weight substance clearances. Some studies suggest that higher clearances decrease mortality, particularly in patients with DM and ESRD, although no prospective studies have yet directly compared these two modalities.

Survival is longer for diabetc patients receiving a living related donor transplant compared to patients remaining on dialysis. Two-year renal graft survival and patient survival in Type I DM with living related donor transplants are comparable to survival in nondiabetic ESRD patients. However, Type I DM patients who receive a cadaveric renal transplant have a higher morbidity and mortality than nondiabetic ESRD patients. Patients receiving combined renal and pancreas transplants have a higher morbidity rate than those undergoing renal transplant alone, but have improved hyperglycemia, and both motor and sensory nerve function. No benefits are demonstrable for pancreatic polypeptide secretion, preservation of kidney function, or retinopathy.

The increased morbidity and mortality rates observed in ESRD patients with DM are mainly secondary to complications of atherosclerotic disease. Many investigators have shown that the risk for cardiovascular disease in diabetic patients with renal disease far exceeds that in duration-matched patients with DM without nephropathy. Other morbidity stems from an excessive rate of cerebral and peripheral vascular complications. Low serum albumin and infection also complicate renal replacement therapy for patients with DM. Thus, despite advances malnutrition, infection, and atherosclerotic diseases shorten the life of the patient with DM and ESRD.

Clinical Manifestations and Diagnosis

Microalbuminuria appears to be an important marker for the development of proteinuria and declining renal function. Current recommendations are that all patients with Type I DM of greater than 5 years duration should be screened yearly for microalbuminuria. It is important to specifically order testing for urinary albumin excretion or microalbuminuria, because of the low sensivity of routine urine protein determinations for this condition [10]. Urinary albumin excretion rates exceed 300 mg/day in patients with proteinuria measured either by dipstick or by the traditional 24-hour urine protein assay. With sensitive assays for microalbuminuria, urinary albumin excretions < 30 mg/24 hour can be detected. Patients with normal kidneys have urinary albumin excretion rates < 30 mg/24 hour or 20 μg/min, while microalbuminuria is defined as albumin excretion rates of 30 – 300 mg/24 hour or 20 – 200 μg/min.

The presence of microalbuminuria can be evaluated in a 24-hour urine collection, an overnight urine collection that can be extrapolated to 24 hours, or a spot urine measurement of the albumin-creatinine ratio (Table 1).

Table 1. Measurement of Microalbuminuria

- Test Type I DM patients of greater than 5 years duration every year.
- Test Type II DM patients at the time of diagnosis and every year.
- Rule out causes of transient microalbuminuria: hyperglycemia, UTI, PE, essential HTN, CHF, water loading.
- If the albumin excretion rate is elevated, repeat 3 times over 3 to 6 months to define persistent microalbuminuria.
- Normal albumin excretion: <30 mg/24 hour; microalbuminuria: 30 – 300 mg/24 hour; proteinuria: >300 mg/24 hour.

UTI: urinary tract infection; PE: physical exercise; HTN: hypertension; CHF: congestive heart failure.

Transient causes of microalbuminuria such as hyperglycemia, urinary tract infection (UTI), physical exercise, uncontrolled hypertension, congestive heart failure, or water loading should be considered. Thus, an elevated albumin excretion rate should be repeated on 3 occasions over 3 – 6 months to confirm persistent microalbuminuria. Patients with Type II DM should be screened at the time of diagnosis and yearly thereafter [12]. Identifying patients with microalbuminuria allows measures to be implemented to slow or halt the progression of their kidney disease much earlier, before significant renal insufficiency develops.

Proteinuria in a diabetic patient warrants evaluation. In patients with Type I DM, the onset of proteinuria occurs between 10 and 25 years after diagnosis. Thus, patients who first present with proteinuria before 10 years or after 25 years duration of DM should be suspected of having another cause of kidney disease. In patients with Type I DM, 90 – 95% of patients with diabetic nephropathy have diabetic retinopathy. Therefore, the absence of diabetic retinopathy as determined by either 7 field fundus photos or fluorescein angiography should again suggest the presence of an alternative diagnosis. Only 60 – 65% of patients with Type II DM and diabetic nephropathy have diabetic retinopathy, making it a less helpful factor in their evaluation. All patients with DM and proteinuria should be evaluated carefully for the presence of other systemic diseases that can cause proteinuria, such as a gammopathy, hepatitis B, systemic lupus erythematosus (SLE) or amyloidosis. Abnormalities in the urinalysis, e.g. hematuria or red blood cell casts, should also alert one to the possibility of another kidney disease. A renal ultrasound will rule out anatomic abnormalities and evaluate the patient for kidney size. Most patients with diabetic nephropathy have large kidneys, especially in relation to their decreased GFR.

In a prospective biopsy series in patients with Type I DM and more recently Type II DM, ≤ 10% of the patients who had the typical clinical features noted above were found to have a diagnosis by biopsy other than diabetic nephropathy. Of those patients with an alternate diagnosis, even fewer had a diagnosis identified for which there was a specific therapy indicated. Thus, in the vast majority of patients with DM and proteinuria, a renal biopsy is not necessary. If, however, the patient has any atypical clinical features as outlined above, a renal biopsy should be performed.

There are unique aspects to the management of the patient with DM and progressive renal insufficiency. Insulin requirements decrease in uremia, both because the kidney is responsible for 30 – 40% of the metabolism of insulin and the loss of appetite as renal function declines. Thus, the majority of patients on insulin will have decreased insulin requirements, and many Type II patients will

have decreased oral hypoglycemic requirements as ESRD nears. Further, many oral hypoglycemic agents are excreted by the kidney, and their half-life is prolonged in patients with renal insufficiency. Thus, it is important to counsel both Type I and Type II patients about hypoglycemia and to monitor their oral hypoglycemic or insulin use. Metformin is contraindicated in patients with serum creatinines greater than 1.5 mg/dL and cannot be used in patients with significant renal insufficiency.

DM is the most common cause of Type IV renal tubular acidosis, which results in hyperkalemia and a hyperchloremic metabolic acidosis. Thus, patients with this tubular transport defect can have an electrolyte pattern that is disproportionately abnormal for the degree of renal insufficiency.

Patients who develop nephropathy frequently have gastroparesis resulting from diabetic neuropathy. Symptoms of gastroparesis such as nausea and vomiting can mimic those of uremia.

It is important to evaluate patients with DM frequently to document the onset of diabetic nephropathy to allow optimal management and preventative measures. Avoiding excessive use of nonsteroidal anti-inflammatory agents, the unnecessary use of aminoglycoside antibiotics, and exposure to IV radiocontrast agents is important. Proper interventions for UTI and neurogenic bladder can also help preserve remaining renal function.

Patients with DM appear to require renal replacement therapy earlier than patients with other renal diseases. They have lower GFRs for any given serum creatinine than nondiabetic patients with renal insufficiency, most likely related to lower muscle mass. It is not uncommon for diabetics to be near ESRD with serum creatinines as low as 2 – 3 mg/dL. Diabetic patients have symptoms of uremia and require the initiation of renal replacement therapy at higher GFR levels than do patients with nondiabetic kidney disease. Choosing the best renal replacement therapy for diabetic patients is complex and requires the consideration of many factors, including their body habitus, vasculature, and extent of atherosclerotic disease and heart function. Lastly, patients with DM have a high prevalence of cardiovascular disease. Thus, transplant evaluation in these patients requires careful cardiac testing. Many of these patients with documented cardiovascular disease also have peripheral vascular disease, which can complicate their course. For all these reasons, dialysis teaching and transplant evaluation should begin early in patients with diabetic nephropathy.

Therapeutic Interventions

The major therapeutic interventions that have been evaluated for patients with diabetic nephropathy include antihypertensive therapy, treatment with ACE inhibitors, improved DM control, inhibitors of AGEs formation, the restriction of dietary protein intake, and treatment of dyslipidemia, as well as a variety of less well-studied interventions (Table 2).

Blood Pressure Control

A close correlation exists between the onset and degree of microalbuminuria and the onset and degree of hypertension. Similarly, the presence of hypertension in patients with proteinuria is associated with a more rapid decline in GFR. Multiple studies have shown that reducing the systemic blood pressure in

Table 2. Therapeutic Interventions in Diabetic Nephropathy

Proven Benefit	Possible Benefit
Blood sugar control Blood pressure control ACE inhibition	Low protein diet Treatment of dyslipidemia Smoking cessation Prevention of AGEs formation

diabetic patients with proteinuria and declining renal function slows the rate of decline of renal function and improves survival. These studies primarily used conventional antihypertensive agents, which at the time did not include calcium channel blockers or ACE inhibitors. Although the studies were performed with relatively few numbers of highly selected patients and achieved only modest blood pressure control, a clearly decreased rate of renal decline was observed. Similarly, in studies of patients with microalbuminuria, reducing the mean arterial blood pressure resulted in decreases in urinary albumin excretion rates. Even in normotensive patients with microalbuminuria, the lowering of systemic blood pressure was associated with decreased urinary albumin excretion.

The definition of adequate blood pressure control in patients with diabetic nephropathy has been unclear. The Fifth Joint National Commission defines high normal blood pressure as 140/90 mmHg, and physicians have traditionally used this as a blood pressure goal for patients with hypertension. A number of epidemiological studies indicate that the progression of renal disease correlates closely with increased systemic blood pressure. This effect was linear, with no lower threshold for the benefits of lower blood pressure. Recently, the Collaborative Study Group randomized patients with Type I DM and proteinuria to 2 levels of blood pressure control (a mean arterial blood pressure < 92 mmHg or to a mean arterial blood pressure of 100 – 107 mmHg) to better define the optimal blood pressure for preservation of kidney function. All patients in this study received an ACE inhibitor (Ramipril). Preliminary analysis of these results suggests that the lower blood pressure goal conferred greater benefit. Indeed, many of the patients with the lower blood pressure did not have demonstrable decline in renal function, but rather a regression in their degree of proteinuria, in some cases to near normal ranges. Thus, available data suggest that the blood pressure goals for protecting the kidney against progressive diabetic nephropathy may be lowered to mean arterial blood pressures < 92 mmHg.

In addition a reduction in urinary protein or albumin excretion might be an appropriate end point of antihypertensive therapy independent of its effect on systemic blood pressure. Several major studies in nondiabetic kidney disease demonstrate that an early reduction in urinary protein or albumin excretion predicts a long-term beneficial effect of the intervention. Thus, it has been suggested that antihypertensive therapy should be advanced as tolerated to help reduce urinary protein excretion.

ACE Inhibition

Data from experiments in diabetic rats first suggested that specific antihypertensive agents (ACE inhibitors) could preserve renal function and structure independent of their effect on systemic blood pressure. In these studies, glomerulosclerosis was only partially mitigated by the use of conventional antihypertensive agents, including hydralazine, re-

serpine and hydrochlorothiazide. However, with ACE inhibitors, albuminuria and glomerulosclerosis were ameliorated. The mechanism of protection was postulated to be the reduction of the tonic constrictor effect of Ang II on the efferent arteriole, leading to lower glomerular intracapillary pressures.

A number of studies were then conducted in humans with diabetic nephropathy. A meta-analysis of antihypertensive therapy in patients with diabetic nephropathy, showed only ACE inhibitors decreased proteinuria and preserved GFR independent of changes in systemic blood pressure.

A recently completed clinical trial of ACE inhibitors randomized 409 patients with Type I DM and proteinuria to receive either Captopril three times per day or placebo [13]. Patients enrolled in this trial had urinary protein excretion rates > 500 mg/day and serum creatinine concentrations ≤ to 2.5 mg/dL [13]. The primary outcome of the trial was the time to doubling of serum creatinine (to ≥ 2 mg/dL), representing a halving of the GFR. The use of Captopril led to a risk reduction of 48% for doubling of creatinine compared to the placebo group. Captopril was equally effective in reducing the risk of doubling of serum creatinine in normo- and hypertensive patients and in African American and Caucasian patients. Its efficacy was not explained by differences in baseline urinary protein excretion or follow-up mean arterial blood pressure. Importantly, patients receiving ACE inhibitors had a risk reduction of 50% in the combined clinical outcome of either death or ESRD. Again, this effect of ACE inhibitors was independent of any effect on systemic blood pressure. There were few adverse effects reported, with no ARF and only 6 hyperkalemic events. Thus, this study convincingly demonstrated that ACE inhibition is renoprotective in both normo- and hypertensive patients with Type I DM and clinically evident proteinuria.

Treatment in patients with early diabetic nephropathy characterized by microalbuminuria has also been demonstrated to have a beneficial effect [14]. Studies in patients with both Type I and Type II DM demonstrated that the use of ACE inhibitors leads to a decrease in the urinary albumin excretion with far fewer patients progressing to overt proteinuria. The consistent finding of a beneficial effect of ACE inhibitors in patients with microalbuminuria strongly suggests that these patients should be considered for such therapy to preserve their remaining renal function. Added benefits of ACE inhibitors are improved insulin sensitivity, and plasma lipid profile.

Far fewer studies have been performed examining the efficacy of calcium channel blockers in patients with diabetic nephropathy [15]. These studies were performed in small numbers of patients, most of whom had Type II DM. Recently, it has been suggested that a combination of ACE inhibitors and calcium channel blockers may be of additional benefit. Further investigation is needed to clarify the role of calcium channel blockers in the treatment of patients with DM and diabetic nephropathy.

Improved Blood Sugar Control

Intensive blood sugar control prevents the development of diabetic nephropathy and ameliorates established diabetic nephropathy in animal studies. In humans, the Stockholm Diabetes Intervention Study and the Diabetes Control and Complications Trial have now conclusively demonstrated that intensive blood sugar control in Type I diabetics can delay the development or slow the progression of diabetic nephropathy [16]. Patients in these trials achieved intensive blood sugar control ($HgbA_1C$ ~7.0%) with insulin deliv-

ered either by an insulin pump or by 3 or more injections daily. These patients had a dramatic decrease in the risk of developing microalbuminuria or progressing from microalbuminuria to proteinuria compared to the patients in the conventional therapy group who achieved hemoglobin A_1Cs of approximately 9%. Intensive blood sugar control in these studies not only dramatically reduced the risk of nephropathy, but also the risk of retinopathy and neuropathy. The chief adverse event associated with intensive therapy was a 2 – 3-fold increase in severe hypoglycemic episodes requiring assistance. These hypoglycemic episodes occurred in the intensive therapy group despite careful study management and support measures beyond what most clinics could provide. Secondary analysis of these studies demonstrated reduced nephropathy risk for any reduction in hemoglobin A_1C levels [17]. This reflects the absence of a threshold effect, indicating that any improvement in blood sugar control achievable in the routine clinical setting would reduce the risk of developing diabetic nephropathy. Thus, all patients with Type I DM should achieve the tightest blood sugar control that can be safely achieved in their clinical setting. In Type II diabetics, however, it has not yet been conclusively demonstrated that glycemic control confers a similar advantage. One relatively small study done in Japan has indicated a beneficial effect of tighter blood sugar control in the Type II population. Tight blood sugar control in this population is very difficult to achieve and may have more associated risks.

Prevention of the Formation of AGEs

It has been demonstrated that AGEs accumulate in tissues of diabetic patients and may, at least in part, be responsible for the end-organ complications of DM [5]. Aminoguanidine is a nucleophilic hydrazine compound that prevents the formation of AGEs and glucose-derived collagen crosslinks in vitro and in vivo. Its use in diabetic rats decreases albuminuria and glomerulosclerosis. Clinical trials using aminoguanidine in patients with Type I and Type II DM and established nephropathy are ongoing. This drug is currently available only in research settings.

Dietary Protein Restriction

In many experimental animal models of renal disease, including DM, high dietary protein intake accelerates the deterioration of renal function. Low-protein diets improve glomerular hemodynamics in animal models by vasoconstriction of the afferent arteriole, resulting in decreased glomerular intracapillary pressures. In humans with DM, low protein diets have been demonstrated to reduce glomerular hyperfiltration, decrease urinary albumin excretion, and slow the rate of decline of renal function. Although, individual studies in patients with DM have enrolled small numbers of patients, a recent meta-analysis supported the efficacy of low protein diets in patients with diabetic nephropathy [18].

Lipid-lowering Agents

Dyslipidemia is common in the diabetic state and worsened by coexistent diabetic nephropathy. Patients with poor glycemic control usually have hypertriglyceridemia. The presence of diabetic nephropathy is associated with higher levels of plasma low-density lipoprotein (LDL) cholesterol and lipoprotein B (Lp(b)), and lower levels of high-density lipoprotein (HDL) cholesterol. In

many animal models of kidney disease, dyslipidemia is implicated in causing direct renal injury and hastening the progression of established renal diseases. Treatment of dyslipidemia in these animals leads to reduced glomerular injury. In humans with diabetic nephropathy, hyperlipidemia has been identified as a risk factor for a more rapid rate of decline in GFR and increased mortality. Recently, several small uncontrolled preliminary studies in diabetic patients with proteinuric renal disease showed that treatment with β-hydroxy-β-methyl glutaryl-COA (HMG-CoA) reductase inhibitors can lead to a stabilization and improvement of renal function [19]. Because dyslipidemia is closely related to the progression of cardiovascular disease, and highly prevalent in diabetics, lipid-lowering agents are recommended, irrespective of their potential effect on diabetic nephropathy.

Miscellaneous Interventions

Smoking is an important risk factor for the development and progression of both diabetic nephropathy and atherosclerotic disease. Smoking cessation is an important part of the management of all diabetics.

A variety of other pharmaceutical interventions have been applied to a small number of patients in preliminary studies or in animal models. Pentoxifyline decreased microalbuminuria and proteinuria in Type I patients in a placebo-controlled trial. This drug induces membrane changes that increase erythrocyte deformability, reducing blood viscosity. Similarly, dipyramadole has been shown to decrease urinary albumin excretions in Type I patients with microalbuminuria. Octreotide, a somatostatin analogue, reduced GFR and kidney size in 11 patients with Type I DM and glomerular hyperfiltration. It has also been shown to decrease urinary albumin excretion and renal hypertrophy in rats with streptozotocin-induced DM. Although the potential mechanism of the beneficial effect is unknown, it may be mediated by inhibition of insulin-like growth factor-1.

Lastly, DM has been characterized by an increase in plasma levels of thromboxane B_2. Thromboxane synthetase inhibitors significantly lower urinary protein excretion in diabetic rats. In a recent randomized, double-masked, placebo-controlled trial in 30 patients with DM and microalbuminuria, picotamide (a dual antithromboxane ag-coent that inhibits thromboxane synthetase and blocks the thromboxane receptor) significantly lowered urinary albumin excretion compared to placebo.

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Comprehensive review of available information on the epidemiology, natural history and efficacy of therapeutic interventions in patients with Type II DM and diabetic nephropathy

[**] The Diabetes Control and Complications Trial (DCCT) Research Group 1995 Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. Kidney Int *47: 1703-1721*

This clinical trial is a conclusive demonstration that intensive glycemic control decreases the risk of developing diabetic nephropathy in patients with Type I DM

[+] *Lewis EJ, Hunsicker LG, Bain RP, Rohde RD for the Collaborative Study Group* 1993 The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. N Engl J Med *329:* 1456-1462

The clinical trial reported in this paper demonstrates the dramatic efficacy of ACE inhibitors in slowing the progression of renal insufficiency in patients with Type I DM and diabetic nephropathy.

The Kidney in Systemic Diseases

Patrick H. Nachman, Ronald J. Falk and J. Charles Jennette

Introduction

When the kidney is involved in a systemic disease process, it may either be the most conspicuously damaged organ or play a minor role in diseases that affect other tissues. The kidney may be injured at the outset of the disease or affected relatively late in the course of the disease. For instance, in some patients with systemic lupus erythematosus (SLE), nephritis is a presenting manifestation of disease. In others, dermatologic and serologic evidence of SLE may predate the onset of renal disease by months to years. In some systemic disorders, the kidney is one of many affected organs, as in primary amyloidosis, which simutaneously affects the heart, liver, and kidney. In some patients, the extra-renal manifestations of systemic injury mirror the course of renal injury, whereas in others, the extra-renal disease may differ with respect to onset, severity, and course. This chapter will consider systemic diseases that frequently involve the kidney, including diseases due to vascular inflammation, infections, liver disease, paraneoplastic syndromes, and dysproteinurias. The systemic diseases that result in tubulointerstitial disease, thrombotic microangiopathy, and cancers of the kidney are discussed in other chapters.

Presentation of Systemic Diseases in the Kidney

The clinical manifestations of many systemic diseases involving the kidney can be divided into major clinical and pathological syndromes, including

- nephrotic syndrome,
- nephritic syndrome,
- tubulointerstitial disorders (covered in Chapter I.8),
- renal-pulmonary syndrome,
- renal-dermal syndrome, and
- liver disorders.

Some systemic disorders consistently present with nephrotic syndrome (e.g. the dysproteinemias) (Table 1), others consistently with the nephritic syndrome (e.g. antineutrophil cytoplasmic autoantibodies (ANCA) small-vessel vasculitis), and still others with features of both syndromes (e.g. SLE).

The clinician should first assess the patient with history and physical examination to determine the scope and nature of the systemic disease process. Laboratory studies, including serological findings, and assessment of complement cascade activation, may increase or decrease the likelihood of certain diseases (Tables 2 and 3). Some diseases activate complement primarily through the classical pathway, resulting in diminution of C4 to a greater

Table 1.

Systemic Diseases that Usually Present with Nephrotic Syndrome

Systemic lupus erythematosus
Dysproteinemias
- Amyloidosis (AL and AA)
- Light chain deposition disease
- Fibrillary glomerular diseases
- Immunotactoid glomerulonephritis

Paraneoplastic syndromes

Cirrhosis
- Focal segmental sclerosis

Infections
- Human immunodeficiency virus (especially in African Americans)
- Syphilis
- Malaria
- Leprosy
- Filariasis
- Toxoplasmosis
- Schistosomiasis (especially *S. mansoni*)

Systemic Diseases that Usually Present with Glomerulonephritis

Systemic lupus erythematosus

ANCA small vessel vasculitis

Henoch-Schönlein purpura

Cryoglobulinemia

Infections
- Hepatitis B, C
- Bacterial pneumonias: Pneumococcus, Staphylococcus, Legionella, Klebsiella, Mycoplasma
- Human immunodeficiency virus (especially in Caucasians)
- Viral infection with Coxsackie, Epstein-Barr, Rubella
- Toxoplasmosis
- Trichinosis

Paraneoplastic Syndromes

Cirrhosis
- IgA glomerulonephritis

extent than C3. In contrast, other disease processes result in activation of the alternative complement pathway, resulting in near-normal levels of C4 but a diminution of C3 (Table 3) [53].

Many systemic diseases that have renal involvement can be grouped in recognizable syndromes, such as renal-pulmonary, renal-dermal, renal-cardiac, or renal-liver syndromes (Table 4). For instance, patients with glomerulonephritis and pulmonary infiltrates or nodules and hemoptysis may fall into the spectrum of a small-vessel vasculitis that affects both the kidney and the lung. In other patients, the presentation of palpable purpura in the lower extremities and nephritis raises the possibility of Henoch-Schönlein purpura (HSP) in a young child, or microscopic polyangiitis or cryoglobulinemia in an adult. Thus, these syndromes provide clinicians with clues to the nature of the systemic disorder.

The clinician should approach a patient who may have a systemic disorder affecting the kidney with the following questions in mind:

- What is the renal presentation of the clinical disorder? Is it predominantly nephrosis, nephritis, or tubulointerstitial disease?
- Are there serologic findings that increase or decrease the likelihood of a specific systemic disease?
- What are the predominant extra-renal organ systems involved by the systemic disease process?
- Is the kidney the dominant organ involved?
- Would a kidney biopsy provide a pathological diagnosis of the disorder?

Frequently, patients with systemic disease are not cared for primarily by nephrologists. When a systemic disease affects the kidney, it may do so in an explosive fashion resulting in a rapid, sometimes irreversible, decline in re-

Table 2. Serologic Findings in Patients with Renal Disease and Systemic Illness

Systemic Illness	Serologic Findings
Systemic lupus erythematosus	ANA/Anti-double-stranded DNA
Small-vessel vasculitis	ANCA
Wegener's granulomatosis	PR3-ANCA > MPO-ANCA
Microscopic polyangiitis	MPO-ANCA > PR3-ANCA
Churg-Strauss syndrome	MPO-ANCA
Cryoglobulemic vasculitis	Mixed cryoglobulins
	Anti-Hepatitis C antibodies
Amyloid (primary amyloidosis)	Lambda monoclonal immunoglobulins
Light chain deposition disease	Kappa monoclonal immunoglobulins
Membranous nephropathy	Infections
	Anti-Hepatitis B antibodies
	Antitreponemal antibodies
HIV nephropathy	Anti-human immunodeficiency virus antibodies
Post-infectious glomerulonephritis	Anti-streptococcal antibodies/anti-DNAse b
Goodpasture's syndrome	Anti-GBM antibodies
Polyarteritis nodosa	Anti-Hepatitis B antibodies
Thrombotic microangiopathy	Anticardiolipin antibodies
Systemic sclerosis	Anti-DNA topoisomerase
Sjögren's syndrome	Anti-RO, anti-LA antibodies
Mixed connective tissue disease	Anti-RNP

Table 3. Complement Profiles in Systemic Disease

Disorders that activate complement primarily through the classical pathway (low C4)
– Systemic lupus erythematosus
– Cryoglobulinemia

Disorders that activate complement through the alternative pathway (low C3)
– Post-infectious disorders
– Post-streptococcal glomerulonephritis
– Infective endocarditis
– Partial or total lipodystrophy
– Atheroembolic emboli

nal function. This is especially true of the small-vessel vasculitides and SLE. In these cases, the nephrologist must ask yet another question.

– Does the rapid decline in renal function require urgent diagnosis and emergency therapeutic intervention?

Vascular Inflammatory Disease

Systemic Lupus Erythematosus (SLE)

Pathology

The diagnosis of SLE is based on combined clinical, pathological, and laboratory findings. The classification of patients with lupus is based on criteria established by the Ameri-

Table 4. Clinical Pathological Syndromes in Systemic Diseases

Renal-pulmonary syndromes
– ANCA small-vessel vasculitis
– Goodpasture's syndrome
– Systemic lupus erythematosus
– Cryoglobulinemic vasculitis
– Progressive systemic sclerosis
Renal-dermal syndromes
– ANCA small-vessel vasculitis
– Henoch-Schönlein purpura
– Systemic lupus erythematosus
– Cryoglobulinemic vasculitis
– Progressive systemic sclerosis
– Infective endocarditis
– Visceral abscesses
Renal-cardiac syndromes
– Infective endocarditis
– Amyloidosis
– Systemic lupus erythematosus
– ANCA small-vessel vasculitis
Renal-liver disorders
– Hepatitis B
– Hepatitis C
– Cirrhosis with:
IgA nephropathy
Focal sclerosis

can Rheumatism Association [97]. To establish a diagnosis of SLE, patients must exhibit at least 4 of the 11 signs or symptoms listed in Table 5. The clinical diagnosis of renal lupus is most likely made following a renal biopsy diagnostic of lupus nephritis in the presence of positive serology and characteristic extrarenal manifestations of disease.

Lupus nephritis is the prototypic immune complex glomerulonephritis. Most, if not all, lupus patients have deposition of immunoglobulin and complement, even if there is no clinically significant renal dysfunction. The location and quantity of immune reactants and the host response to these immune reactants results in a spectrum of renal lesions categorized by the World Health Organization (WHO) into different classes of lupus nephritis.

WHO class I (absence of pathologic lesion) is the mildest pathologic expression of lupus nephritis. Class II lupus nephritis is a consequence of immune complex localization confined to the mesangium. The deposits are readily identified in all mesangial regions by immunofluorescence and electron microscopy. By light microscopy, there may be no identifiable glomerular lesions (class IIA), or varying degrees of focal to diffuse mesangial hypercellularity (class IIB). Class II lupus nephritis usually causes only a mild nephritic picture with asymptomatic hematuria and proteinuria.

When nephritogenic immune complexes are deposited not only in mesangial but also in subendothelial regions of the glomeruli, they result in increased inflammation. This results in focal proliferative (class III) or diffuse proliferative (class IV) lupus nephritis. The glomerular lesions are characterized by complex endocapillary hypercellularity caused not only by mesangial and endothelial proliferation, but also by leukocyte infiltration. The most active lesions are complicated by necrosis and crescent formation. Because SLE is often a persistent, although relapsing and remitting, disease, inflammation usually results in chronic changes, such as glomerular sclerosis, adhesions, fibrous crescents, interstitial fibrosis, and arteriosclerosis. The relative histologic markers of active inflammation and chronic injury can be expressed as activity and chronicity scores, the prognostic importance of which is controversial [4].

When capillary wall immune complexes are localized predominantly in the subepithelial zone rather than the subendothelial

Table 5. ACR Criteria for Systemic Lupus Erythematosus

Criteria	Description
Malar rash	Flat or raised erythema
Discoid rash	Scaly, erythematous plaques
Photosensitivity	Sun-induced or exacerbated rashes
Oral ulcers	Ulcerations of mucous membrane
Arthritis	Nonerosive, nondeforming arthritis of small joints
Serositis	Pericarditis or pleuritis
Renal disorders	Proteinuria greater than 500 mg/day or cellular casts
Neurological disorders	Seizures or psychosis
Hematologic disorders	Hemolytic anemia, leukopenia, lymphocytopenia, or thrombocytopenia
Immunologic disease	Positive LE test, anti-double-stranded DNA antibodies, anti-SM antibody, or false-positive serologic test for syphilis (STS)
Anti-nuclear antibody	Abnormal titer (in absence of predisposing drugs).

Modified from Tan EM et al. Arthritis Rheum 1982; 25:1271-1277 with permission.

zone, they are not in direct contact with circulating inflammatory mediators, and a membranous glomerulonephritis results (class V lupus nephritis). Class V lupus nephritis tends to cause more nephrotic than nephritic disease, unless there is a substantial proliferative component along with the membranous pattern. Specimens with exclusively membranous changes are sometimes designated class Va, those with concurrent mesangial hypercellularity Vb, those with concurrent focal endocapillary proliferative changes Vc, and those with concurrent diffuse proliferative changes as Vd. In essence, so-called class Vd lesions are a combination of class IV and class V lesions and thus have massive accumulations of mesangial, subendothelial, and subepithelial immune complexes. Patients with class Vc and Vd lupus nephritis follow a clinical course resembling that of focal or diffuse proliferative lupus glomerulonephritis (class III and IV), whereas patients with class Va and Vb have a predominantly nephrotic course. Therefore, it is our bias to treat patients with combined membranous and proliferative lesions (class Vc and Vd) as if they had class III or IV lupus nephritis.

Several types of vascular abnormalities can be found in the setting of lupus nephritis. The most common is an arteriolopathy caused by accumulation of immune complexes in the walls of hilar arterioles without induction of overt vasculitis. True vasculitis with mural infiltration by leukocytes is rare. The presence of hypertension, which may reach the malignant range in aggressive lupus nephritis, leads to typical hypertensive arterial and arteriolar changes. Some lupus patients develop a thrombotic microangiopathy, possibly associated antiphospholipid antibodies or an overlap with systemic sclerosis. This complication is characterized by subendothelial expansion in glomerular capillaries, fibrinoid necrosis of arterioles, and edematous intimal expansion in arteries. The resultant narrowing of lumens, as well as superimposed thrombosis, can cause severe and rapid renal failure and microangiopathic hemolytic anemia.

One difficulty of managing a patient with lupus nephritis is that the pathological lesion may change from one form of glomerular injury to another. It is common for a class III lupus nephritis to progress to a class IV lupus nephritis. Both class III and class IV lesions can transform into membranous lupus nephritis, either spontaneously or with immunosuppressive therapy. It is less common, but possible, for membranous lesions to transform into more proliferative lesions. Even repetitive clinical evaluations may not be sufficiently insightful, and repeated renal biopsies are sometimes needed.

The Role of Renal Biopsy

The pathologic manifestations of lupus nephritis span the spectrum from mild mesangial proliferation to severe necrotizing and crescentic glomerulonephritis. The array of clinical findings may range from intermittent episodes of hematuria and proteinuria to acute nephritis with renal insufficiency, and from mild elevations of creatinine, proteinuria, hypertension, and hematuria (with or without red cell casts) to a picture compatible with rapidly progressive glomerulonephritis. As progressive glomerular sclerosis and interstitial fibrosis ensue, fixed proteinuria develops, as does reversible renal insufficiency. The nephrotic syndrome commonly occurs and is usually associated with either class V lupus nephritis or with chronic proliferative disease that has developed focal glomerular sclerosis, which is also typically associated with renal insufficiency. In fact, the nephrotic syndrome may be the predominant clinical manifestation of disease in fully half of lupus patients with renal involvement. At the time of initial presentation, 20 – 25% of patients with SLE already have some degree of renal insufficiency. The clinician faces the question of whether proteinuria is a consequence of membranous nephropathy, diffuse proliferative glomerulonephritis, or chronic disease with extensive glomerular sclerosis. Furthermore, in some patients, there is a dissociation between the pathological and clinical features of the disease. Patients may present with severe extra-renal SLE and a picture of acute nephritis, but only have mild class II lesions by biopsy. In others, a diffuse proliferative glomerulonephritis may present clinically with only minimal degrees of hematuria and proteinuria.

One of the most difficult clinical pictures is that of a patient with long-standing lupus nephritis and a history of intermittent episodes of nephritis, who develops a rising serum creatinine. In these individuals, it is not always clear whether the renal insufficiency is caused by progressive glomerular and interstitial scarring or by the recrudescence of active nephritis.

The role of a renal biopsy in the evaluation of patients with systemic lupus erythematosus and nephritis has been extremely controversial. Extensive debate continues concerning the correlation between pathologic findings of classic lupus nephritis, the activity of the injury, the degree of chronic changes, and long-term outcome [6]. In our view, the renal biopsy helps to clarify the clinicopathologic syndrome. The biopsy allows for a reasonable separation of membranous lupus from predominantly proliferative disease. It may also restrain the impulse for immunosuppressive therapy in individuals with marked renal insufficiency and proteinuria, who on pathologic examination have only chronic disease with extensive glomerular sclerosis, but no active inflammation. The renal biopsy can be a key factor in determining if a rise or decline in renal function is a consequence of recrudescence of active inflammation or of progressive glomerular sclerosis. Similarly, it

is important to perform a renal biopsy for a patient with lupus nephritis who suddenly develops acute decompensation in renal function. The biopsy will determine whether this sudden deterioration is caused by worsening of the lupus nephritis (e.g. with extensive crescentic formation), the development of a thrombotic microangiopathy (possibly associated with antiphospholipid antibodies), or the development of a process not directly caused by lupus (e.g. tubulointerstitial nephritis caused by the use of an antibiotics or nonsteroidal anti-inflammatory drug (NSAID)).

Laboratory Studies

Antinuclear antibodies (ANA) are more than 90% sensitive for SLE but are only 70% specific. These antibodies are also found in patients with other rheumatic diseases, with infections, and in older age groups. In contrast, up to 10% of patients who fulfill the ACR criteria for lupus do not have a positive ANA. A proportion of ANA-negative patients actually have a positive ANA, if HEp-2 or Kb culture cell lines are used as the target substrate.

Tests for antibodies to nuclear or cytosolic antigens other than DNA are more specific for SLE. For example, antibodies to the SM antigen, one of the so-called extractable nuclear antigens (ENA), are very specific for lupus but found in only 25% of patients. It has been suggested that patients with anti-Sm antibodies have a higher risk of severe lupus, renal disease, CNS disease, cutaneous vasculitis, and death [7, 8].

Complement studies are frequently performed in patients with lupus, both for diagnosis and to measure disease activity. The total hemolytic complement (CH50), as well as C4 and C3, are typically low during active disease. Because decreased synthesis of complement components also results in depressed complement levels, a depressed complement value may not always indicate active disease. Repeated analysis of these factors may provide an insight into the relative state of complement activation.

Prognosis

There is a general assertion that the long-term survival of patients with SLE has improved over last 50 years. Some of this progress is a consequence of the broadened appreciation of the picture of SLE, and some may be attributed to the judicious use of corticosteroids and the introduction and refinement of the use of cyclophosphamide and azathioprine. Overall, lupus mortality is still more likely to result from cerebritis or myocarditis than a loss of renal function, largely due to the availability of dialysis and transplantation. The other major cause of death is overwhelming infection after immunosuppressive therapy.

Certain prognostic factors affect the long-term outcome of renal disease. In a recent study of patients with diffuse proliferative glomerulonephritis treated with cyclophosphamide, poor outcome was more likely for black patients and for those whose biopsies revealed interstitial fibrosis [32]. Using multivariate analysis, black race was a more significant predictor of poor outcome than the entry serum creatinine. From the available data, it was not clear why black patients fared poorly. Hypertension and the rapidity of diagnosis do not appear to be critical variables in these analyses. Whether the poor prognosis is a consequence of a genetic factor or of a lower socioeconomic status is not certain and is the subject of ongoing investigation.

In other studies, the entry serum creatinine [6] and the biopsy findings have been suggested as predictors of eventual renal failure. While no specific numerical cutoff on the chronicity index scale is invariably associated to long-term outcome, it is reasonable to suggest that individuals with substantial interstitial fibrosis, glomerulosclerosis, and tubular atrophy will progress to end-stage renal disease (ESRD) over the course of years, especially if they suffer additional episodes of active inflammation.

Patients with lupus membranous glomerulonephritis (WHO class Va and b) appear to follow a similar course to that of patients with idiopathic membranous nephropathy [82]. Patients with WHO class Vc and d with proliferative glomerulonephritis, necrosis and crescent formation have a similar course to those with aggressive Class IV disease. In our view, classifying cases of severe diffuse proliferative glomerulonephritis in the setting of lupus membranous nephropathy as Class V (c and d) lupus has only served to confuse the nomenclature and clinical evaluation of the disease process. Certainly, membranous nephropathy can transform to a diffuse proliferative glomerulonephritis and result in a worse prognosis for the patient. In a study by Sloan [92], a group of 79 patients with lupus membranous nephropathy were examined and divided into 3 groups:

- (1) WHO class Va and Vb,
- (2) WHO class Vc (with <50% glomeruli involved), and
- (3) WHO class Vc (with >50% glomeruli involved) and Vd.

At the end of five years, the renal survival was 86%, 72%, and 49% in each of these 3 groups respectively, and 72%, 48%, and 20% at 10 years. The entry serum creatinine was the only clinical predictor of renal outcome.

Treatment Issues

Few areas of medicine generate as much discussion and controversy as does the subject of therapy for SLE and lupus nephritis. Whether patients should be treated only with corticosteroids, with intravenous cyclophosphamide, or with oral cyclophosphamide or azathioprine has never been truly resolved. Nor is it resolved whether corticosteroids should be used in high-dose oral form, as some have asserted a role for parenteral methylprednisolone (pulse methylprednisolone). Rarely has an identical protocol been employed in different uncontrolled – or even controlled – trials. Despite the morass of conflicting literature, the general practice of nephrologists has been altered by several investigations from the National Institutes of Health in the mid-1980s. These studies promulgated the beneficial effects of combined prednisone with parenteral cyclophosphamide, oral cyclophosphamide or oral cyclophosphamide and azathioprine [6]. More recently, Boumpas et al. [13] conducted a prospective trial treating patients with severe diffuse proliferative glomerulonephritis with either pulse methylprednisolone alone or either a long or short course of cyclophosphamide. The short course involved either three pulses of intravenous methylprednisolone or monthly pulses of intravenous cyclophosphamide for six months. In the long course, six months of monthly pulses of intravenous cyclophosphamide were followed by a dose every three months for two years. Similar amounts of corticosteroids were used. After 5 years of follow-up, the pulse methylprednisolone group experienced a doubling of the serum creatinine in almost half of the patients, and 25% developed ESRD. In the short-course cyclophosphamide group, the serum creatinine doubled in one third of the patients; 25% also developed ESRD. In the long-

course cyclophosphamide group, the serum creatinine doubled in only 15% of the patients and only 10% developed ESRD.

The most prominent side effects of this form of therapy are infection, ovarian failure (especially inpatients treated with long-course cyclophosphamide), bone disease, and cataract formation. The incidence of malignancies (especially bladder cancer) with this form of therapy is not known. Studies of long-term oral cyclophosphamide treatment for patients with Wegener's granulomatosis suggest that 15% of patients will develop transitional cell carcinoma of the bladder over the course of 5 to 10 years [100]. The rate at which patients with lupus nephritis treated with intravenous cyclophosphamide (which is associated with a smaller incidence of hemorrhagic cystitis than the oral form) will develop bladder cancer is not yet ascertained.

Our own studies of patients with diffuse proliferative glomerulonephritis reveal that Caucasian patients treated with intravenous cyclophosphamide have an excellent 5-year survival rate (95%), compared to only 57% at 5 years in blacks [32]. It is thus likely that the controversy about optimal treatment of patients with lupus nephritis stems in part from the enrollment of patients of different ethnicity, degrees of renal insufficiency, and WHO classifications of nephritis [5].

Because patients with lupus nephritis are frequently young women, the development of ovarian failure is of a substantial worry [72]. Whether there are forms of therapy that can protect the ovary is not yet known. Studies using leuprolide acetate to induce a temporary state of ovarian shutdown are under way. The results, and the usefulness of high-dose estrogen and progesterone are still unknown.

The best approach to therapy relies on an assessment of several factors. The clinician should assess disease activity, disease severity, the patient's previous history of disease activity, and the patient's own response to corticosteroid and immunosuppressive drugs.

The clinician must differentiate between disease severity and disease activity. Disease severity may be a consequence of previous organ system dysfunction, e.g. previous glomerular crescent formation and subsequent glomerular scarring. There can be severe renal damage that is no longer amenable to immunosuppressive therapy. In contrast, active disease may respond to corticosteroids and immunosuppressive activity. There have been several attempts at quantitating organ system dysfunction, including the development of a damage index [44].

There are several markers of disease activity. The clinical history is usually most helpful for assessing overall symptomatology. Renal disease activity may be indicated by numerous red cells and red cell casts found on urinalysis. The presence of proteinuria may relate to previous renal damage rather than to an acute process, except in cases of membranous nephropathy and its attendant nephrotic syndrome. Overall lupus activity may be ascertained by using serological markers as adjunctive tests. Rises in the anti-double-stranded DNA titer, or declines in complement levels, especially CH50, are particularly helpful. Nonspecific markers of disease activity, such as erythrocyte sedimentation rate or the C-reactive protein, are probably no more useful than an overall "sick index". There has been some interest in differentiating rises in C-reactive protein levels during infections from rises that occur during episodes of inflammation. Nonetheless, there are patients with clear evidence of renal exacerbation who do not have hypocomplementemia or elevated levels of anti-DNA antibodies. When there is a progressive rise in serum creatinine and development of significant hematuria, patients more than likely have aggressive renal disease. A renal biopsy is particularly useful for patients

with a history of a prior episode of glomerulonephritis and immunosuppressive treatment. The finding of widespread glomerular scarring, interstitial fibrosis, and tubular atrophy in a patient with moderate renal insufficiency may result in a less aggressive approach then when active inflammation is found with lesser amounts of sclerosis.

Treatment Recommendations

Our treatment strategy is based on persistent supportive management, including careful attention to blood pressure and nutrition, and a prophylactic approach to the surveillance and treatment of infections. Attention to the development of osteoporosis is considered in all patients. In nonrenal-failure patients having received any prednisone at all, specific recommendations include 1.2 grams of calcium/day. If the patient then has evidence of osteoporosis by bone densitometry scanning (T scores that are 2 standard deviations below the mean), use of an antiresorber (alendronate or calcitonin) is recommended. However, if the creatinine clearance is less than 50mL/min, alendronate would not be used. The specific recommendation for treatment of musculoskeletal complaints is the use of nonsteroidal anti-inflammatory agents and an anti-malarial (plaquenil) for mild to moderate arthritis or dermatitis.

We treat major episodes of Class III and IV glomerulonephritis with cyclophosphamide and prednisone. Prednisone is given at a dose of 1 mg/kg/day for the first month, leading to alternate-day doses in the second month. Each week, the prednisone dose is lowered by 10 mg every other day, (e.g. 60 mg alternating with 50 mg every other day, followed by 60 mg alternating with 40 mg one week later). Frequently, extra-renal manifestations of the disease require the continued use of daily oral prednisone at doses between 5 and 10 mg/day. Once patients reach a dose of 10 mg/day, the dose of prednisone is decreased by 1 mg/month until the corticosteroid dose is zero.

In the patient presenting with crescentic lupus diffuse proliferative glomerulonephritis (WHO class IV), pulse methylprednisolone is given at 7 mg/kg on 3 consecutive days. Intravenous cyclophosphamide is given according to the National Institutes of Health protocol, once a month for 6 consecutive months. The dosage is determined on the basis of the leukocyte nadir; the white count should not sink below 3000 cell/mm^3. The dosage is titrated upward during the first 6 months, starting at a dose of 0.5 g/m^2 body surface area and increasing by 0.25 g/m^2 on successive treatments, provided that the 2-week leukocyte count is acceptable. The dosage never exceeds 1 g/m^2. After the first 6 months, the NIH long-course therapy is used; then consolidating treatments, every 3 months for a total of 24 months. Patients with significant renal impairment (serum creatinine > 4 mg/L) may need a reduction in the first dose of parenteral cyclophosphamide.

For patients with focal proliferative glomerulonephritis (WHO class II and III), it is most difficult to determine when treatment is needed. Most patients are treated with corticosteroids for their extra-renal manifestations of disease. Whether additional high-dose prednisone, cyclophosphamide, or azathioprine is indicated for focal proliferative disease is not clear. However, when there is necrosis or crescent formation in addition to the focal proliferative disease, and when 50% of glomeruli are affected, the long-term outcome is probably similar to that of diffuse proliferative glomerulonephritis (Class IV) and should be treated in the same fashion.

Since the renal prognosis of membranous WHO Class Va or b lupus is usually excellent, a trial of corticosteroid therapy should only be considered in certain individuals. In patients with severe debilitating nephrotic syndrome or declining renal function, it may be useful to employ both corticosteroid and even cyclophosphamide therapy. It is not clear whether the degree of proteinuria represents an additional risk. The role of cyclosporine is under investigation. In our experience, patients treated with cyclosporine have a high relapse rate when therapy is discontinued.

Careful attention must be paid to the development of serious infection during the first few weeks of treatment. The results of a recent study by Ward [105] evaluated the cause of death in a cohort of 408 patients with systemic lupus erythematosus, 144 of whom died. Deaths were a consequence of lupus activity in 34%, 22% died of infections, 16% of cardiovascular disease, 6% of cerebral vascular disease, and 6% of cancer. Alarmingly, deaths due to lupus and to infection were more common in the younger age groups, whereas deaths due to cancer were more common in older patients. Patients at substantial risk for infection are those treated with pulse methylprednisolone, corticosteroids, and cyclophosphamide. Careful attention is given to avoid side effects of gastric complaints by avoiding the concomitant use of nonsteroidal anti-inflammatory drugs and corticosteroids, with or without the use of H_2 receptor blocking agents. The association of lupus with cancer is not solely attributable to the use of immunosuppressive agents; there may be a risk of lymphoma and other cancers in patients with lupus who have not received immunosuppressive therapy. The most effective way to diminish the side effects of therapy is to terminate the immunosuppression as soon as possible.

Ascertaining the effectiveness of immunosuppressive therapy may be difficult. Evidence for a substantial reduction in the number of urinary red blood cells or red cell casts, or at least stabilization of renal function, are the best indicators of response. Whether there is value to normalizing the CH50 or anti-double-stranded DNA antibodies is a matter of debate, although such normalization portends a favorable long-term outcome.

Plasmapheresis

Plasmapheresis is clearly not indicated in this population. The national cooperative prospective study randomly assigned patients to receive prednisone or cyclophosphamide, with or without plasma exchange [70]. The study failed to demonstrate any benefit of plasma exchange with respect to renal survival or overall survival. Whether other approaches using plasma exchange are efficacious, such as the synchronous use of plasmapheresis with pulse cyclophosphamide, is under investigation [34].

Treatment of Resistant Lupus

In many patients, existing treatment protocols with prednisone and cyclophosphamide are less successful, particularly patients of the black race [32]. One approach has been to use mycophenolate mofetil by itself or with corticosteroid treatment. The efficacy of this drug has been evaluated in two uncontrolled pilot studies, including one of our own for patients with resistant lupus nephritis [52, 77]. Some degree of clinical stabilization has been observed, but these studies are too small and too preliminary to draw conclusions. Two other

approaches have been evaluated in an anecdotal fashion. Pooled intravenous immunoglobulin and total lymphoid irradiation are promising approaches that have not been systematically evaluated.

There are several novel therapies currently under investigation, including lupus tolerogens, anticytokine antibodies, antibodies to the CD40 ligand, and antibodies to the fifth component of complement (anti-C5 antibodies). At this time, these trials are either beginning or are under way, and the utility of any of these agents remains to be determined.

Antiphospholipid Syndrome

In some patients, the antiphospholipid antibody syndrome is associated with SLE [38, 43]. Three types of antiphospholipid antibodies have been characterized, including lupus anticoagulants, anticardiolipin antibodies, and antibodies that cause a false-positive Venereal Disease Research Laboratories (VDRL) test. Patients with these antibodies may develop both arterial and venous thrombosis, thrombocytopenia, or thrombotic microangiopathy. (The diagnosis may be elicited on careful past history of patients who have experienced recurrent fetal loss.) In addition to their lupus, these patients develop glomerular and vascular thrombi. Renal involvement is characterized by fibrin thrombi in small arteries, and glomerular capillaries. Unfortunately, immunosuppresive therapy is usually not effective in reducing the level of antiphospholipid antibodies. Therefore, it is useful to continue long-term anticoagulation therapy with Warfarin, especially for patients with pathological confirmation of glomerular thrombi. It is not clear whether there is a correlation between the use of anticoagulants and renal outcome for patients with lupus.

Small-Vessel Vasculitis (SVV)

Nomenclature of SVV

The nomenclature of small-vessel vasculitis (SVV) has a rich and interesting history and has recently been reviewed [106]. The most recent approach is that proposed by the Chapel Hill Nomenclature Conference, the details of which can be seen in Table 6 [61]. Pauci-immune forms of SVV are microscopic polyangiitis, Wegener's granulomatosis, or the Churg-Strauss syndrome. These different forms of SVV have several similarities, not only on the basis of the blood vessels that they involve (predominantly capillaries, venules, arterioles, and small arteries), but also with respect to the clinical phenotype of the diseases and their association with ANCA.

Pathology

The characteristic feature of the glomerular lesion in SVV is a focal necrotizing glomerulonephritis. Associated with the necrotizing lesions are cellular or fibrocellular crescents that usually involve 50 – 100% of glomeruli. The glomerulonephritides associated with ANCA SVV and antiglomerular basement membrane (anti-GBM) disease are characterized predominantly by necrosis rather than hypercellularity. The reverse is true for immune complex glomerulonephritis, which tends to have prominent proliferative changes. Identification of vasculitis in vessels other than glomerular capillaries is seen in only approximately 10% of renal biopsies from patients with ANCA SVV. Occasionally, "sausage-shaped" pseudoaneurysms are observed within the small arteries of patients with small-vessel vasculitis. Interstitial necrotizing granulomatous inflammation is

Table 6. Names and definitions of vasculitis adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

	Large-Vessel Vasculitis
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 40.
	Medium-Vessel Vasculitis
Polyarteritis nodosa (classic polyarteritis nodosa)	Necrotizing inflammation of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.
Kawasaki disease	Arteritis involving large, medium and small arteries, and associated with mucocutaneous lymph node syndrome. *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.*
	Small-Vessel Vasculitis
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small-to medium-sized vessels (capillaries, venules, arterioles and arteries).
Churg-Strauss Syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and blood eosinophilia.
Microscopic polyangiitis (microscopic polyarteritis)	Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present.
Henoch-Schönlein purpura	Vasculitis with IgA-dominant immune deposits affecting small vessels (capillaries, venules, or arterioles).
Essential cryoglobulinemic vasculitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Modified from Jennette JC, Falk RJ, Andrassy K et al. Nomenclature of systemic vasculitides: the proposal of an international consensus conference. Arthritis and Rheumatism 37:187-192, 1994, with permission.

rarely observed in renal biopsies from patients with Wegener's granulomatosis. Bowman's capsule is frequently disrupted in the inflammatory process and induces a somewhat granulomatous periglomerular inflammation. However, this is a relatively nonspecific reaction that occurs with any form of severely necrotizing glomerulonephritis. Some patients do not have any identifiable glomerular lesions, but rather have tubulointerstitial nephritis or a medullary peritubular leukocytoclastic angiitis.

The necrotizing glomerulonephritis heals with regions of focal sclerosis. In any biopsy specimen, it is possible to observe both acute necrotizing lesions and chronic lesions asso-

ciated with focal sclerosis. The cellular crescents first heal in fibrocellular and then fibrous crescents, resulting at times in complete obliteration of the glomerular tuft. The tubulointerstitial compartment develops interstitial fibrosis and tubular atrophy along with interstitial infiltration by chronic inflammatory cells.

Most patients with ANCA glomerulonephritis and SVV have little or no glomerular staining for immunoglobulin by immunofluorescence microscopy (i.e., they have pauci-immune disease). On electron microscopy, there are often no electron-dense deposits or only a few scattered small deposits within the mesangium. However, it is important to realize that some patients appear to have necrotizing ANCA-glomerulonephritis concurrent with anti-GBM disease or immune complex disease, in which case there is a well-defined background linear or granular staining for immunoglobulins.

Clinical Manifestations

Most patients with ANCA SVV present with constitutional findings such as fever, myalgias, arthralgias, and malaise. The majority of patients describe a flu-like prodrome early in the course of their disease that may occur within days or weeks prior to the onset of their illness. The flu-like prodrome is statistically more frequent in late fall, winter, and spring than in the summer months [35]. Arthralgias, especially a migratory polyarthropathy involving small and large joints, is a frequent prodrome to the clinical presentation of SVV. About 10% of patients will have a frank arthritis with synovial thickening and erythema of the joint.

The renal manifestations of necrotizing glomerulonephritis are hematuria, with or without red cell casts, and proteinuria that can at times be mild to moderate (< 1 to 2 g), or of nephrotic range (as much as 16 g) [90, 91]. Patients may first present with an acute nephritis that is manifested by hematuria, proteinuria, hypertension and renal insufficiency. One of the most common presentations of necrotizing glomerulonephritis is a rapidly progressive glomerulonephritis associated with rapidly-rising creatinine, hematuria, proteinuria, and hypertension. These cases will progress to ESRD if the individuals are not treated emergently.

Alternatively, some patients have clinically undetectable episodes of focal necrosis and hematuria, undergo a remitting and relapsing course which results in the development of substantial glomerulosclerosis and a picture most compatible with chronic glomerulonephritis. Episodes of focal necrosis may resolve by themselves with a loss of hematuria (and red cell cast formation), resulting in proteinuria associated with the pathological finding of focal sclerosing glomerulonephritis. These individuals usually do not respond well to immunosuppressive therapy and eventually require dialytic support.

Some patients present with a renal-dermal vasculitic syndrome. The most common lesion consists of a leukocytoclastic angiitis with purpuric lesions in the lower extremities. However, several other cutaneous lesions have been observed, including ecchymoses, erythematous tender nodules, focal necrosis, ulceration, and livido reticularis. Interestingly, a picture of urticaria that may have been previously treated with antihistamines is also a manifestation of ANCA SVV. This must be differentiated from hypocomplementemic urticarial vasculitis in which there is a depression of C3 and C4.

Pulmonary disease is found in 50% of patients with ANCA SSV and glomerulonephritis. The spectrum of pulmonary lesions varies

from focal infiltrates that wax and wane, to alveolar infiltrates associated with hemoptysis and, in the extreme, to fulminate hemorrhagic alveolar capillaritis resulting in life-threatening massive pulmonary hemorrhage. In many instances, a prodrome of waxing and waning infiltrates, with or without hemoptysis, may antedate the more fulminate phase of disease by months to years. Patients may have been treated with antibiotics with the presumption of bacterial pneumonia, only to discover that the pulmonary process was not affected by this form of therapy. In patients who have a granulomatous component to their disease (that is, Wegener's granulomatosis or Churg-Strauss syndrome), more nodular and occasionally cavitary lesions are found. These nodules and cavities may be very small and only found on spiral CT scans, but they are frequently large enough to be observed by routine chest x-rays. In Churg-Strauss syndrome, pulmonary involvement is the most predominant form of the disease and is associated with asthma and eosinophilia. The acute inflammatory and necrotizing pulmonary lesions evolve into chronic, nonspecific, sclerotic lesions, such as interstitial fibrosis, organized intra-alveolar fibrosis, and bronchiolitis obliterans.

Of the clinical manifestations of ANCA SVV, the upper respiratory tract is the most difficult to diagnose and treat. The vascular inflammation of upper respiratory tract lesions may include nasal erosions, ulcers, and necrosis of the nasal septum. Patients may have serous otitis with involvement of the middle ear and entrapment of the seventh nerve, resulting in facial paralysis. Sinusitis is found in one-third of patients, typically involving more than one sinus cavity, resulting in a picture of pansinusitis. Patients with Wegener's granulomatosis may have bony erosion into surrounding areas, including the orbit. The encrusting of the nasal cavity is difficult to differentiate from concomitant infection, especially in those who have been treated with immunosuppressive therapy. Patients with Wegener's granulomatosis may also have tracheal inflammation, especially in the subglottic region, resulting in stridor. When this subglottic region is profoundly inflamed, critical airway narrowing may ensue, requiring emergency tracheotomy. These lesions are difficult to treat with corticosteroids and cyclophosphamide and may have a relapsing course.

Approximately one-third of patients with ANCA SVV and glomerulonephritis have abdominal complaints, largely similar to those of patients with peptic ulcers that are not amenable to conventional ulcer disease management. In fact, some of these patients have nonhealing gastric ulcers due to vasculitis that only respond to immunusuppressive therapy. These lesions raise a diagnostic challenge for clinicians in differentiating whether they are the result of vasculitis or of corticosteroid therapy. Biopsy of the affected tissue may provide an insight into the pathogenesis. Other sources of abdominal complaints are due to pancreatic inflammation with elevations of amylase and lipase.

The most catastrophic abdominal complication of small-vessel vasculitis is involvement of small arteries or arterioles in the small or large bowel. Such involvement causes transmural ischemic ulcers and bowel perforation resulting in polymicrobial sepsis and bacterial peritonitis. It is important to note that ANCA SVV may also involve the renal, celiac, and mesenteric arteries. Thus, some patients may have aneurysmal formation of these vessels, resulting in bowel wall, renal, or liver infarction.

One quarter of patients with ANCA SVV and glomerulonephritis will develop a neurological disease. This may be a mononeuritis multiplex that results in focal peripheral neu-

ral lesions with either sensory or motor deficits. Rarely, patients may present with seizures as a result of central nervous system vasculitis.

Cardiac disease is uncommon in patients with small vessel vasculitis, but when it does occur, there are two different clinical phenotypes. One is the development of pericarditis with the clinical picture of a serositis-type chest pain. The other phenotype is coronary artery disease as a consequence of vasculitis that results in either subendocardial or transmural myocardial infarctions. Since the average age of patients with ANCA SVV is 55 years, it is difficult to differentiate atherosclerotic coronary artery lesions from those attributable to vasculitis. Other vascular beds can also be affected by ANCA SVV, including the eye. Patients may have iritis or uveitis resulting in red eyes that may or may not be painful. These subtle changes are discernible only by slit lamp examination by an ophthalmologist.

Serology

Approximately 90% of patients with ANCA SVV have either a myeloperoxidase ANCA (MPO-ANCA) or a proteinase 3 ANCA (PR3-ANCA) [48]. MPO-ANCA is predominant in patients with microscopic polyangiitis and the Churg-Strauss syndrome, or with necrotizing and crescentic glomerulonephritis without extrarenal manifestations. PR3-ANCA predominates in patients with Wegener's granulomatosis. Nonetheless, 20 – 30% of patients with Wegener's granulomatosis will have an MPO-ANCA, and approximately 20 – 30% of patients with necrotizing glomerulonephritis with no obvious extrarenal manifestations will have a positive PR3-ANCA. Most patients have normal complement levels, and approximately 10% of patients have a positive ANA.

Prognosis

The long-term prognosis of patients with ANCA SVV depends on two different variables. Mortality is largely related to the occurrence of massive pulmonary hemorrhage, which accounts for at least half of all deaths in the fulminant phase of disease. The long-term renal prognosis is largely associated with the entry serum creatinine [54]; the higher the serum creatinine, the higher the risk of developing ESRD. The combined pathological activity and chronicity indices may also play a prognostic role in patients with substantial active disease.

Treatment Recommendations

Treatment of ANCA SVV can be divided into three phases: induction, maintenance of remission, and treatment of relapse before tissue destruction occurs [78].

Several protocols have been used for induction therapy. Our approach is to use intravenous methylprednisolone at a dose of 7 mg/kg on 3 consecutive days, especially for patients with renal and pulmonary involvement. The use of plasmapheresis has been promulgated largely in Europe, especially in Great Britain, where the vast majority of patients with SVV receive this form of therapy [84]. The relative benefits of intravenous methyl prednisolone versus plasmapheresis are the subject of an ongoing clinical investigation.

To complete the induction therapy, all patients are given 1 mg/kg/day of prednisone for one month. Corticosteroids are then tapered

to an alternate-day regimen during the second month of treatment and eventually discontinued by the end of the fourth or fifth month.

Once induction therapy is complete, there are 3 options for immunosuppressive therapy. The first approach is to use intravenous cyclophosphamide on a monthly basis, given at a dose of 0.5 g/m^2. The dosage is adjusted on the basis of the 2-week leukocyte nadir in order to affect a leukocyte count of 4000 cells/mm^3. In some cases of especially severe systemic vasculitis, the initial dose may be repeated at week 3 if the symptoms of the vasculitis are breaking through high-dose prednisone therapy. A second alternative is to use oral cyclophosphamide, given at a dose of 2 mg/kg/day [55]. To prevent severe leukopenia, careful attention to the leukocyte count must be maintained throughout this therapy. The patient must be admonished to drink plenty of fluids, because adequate diuresis is essential to avoid hemorrhagic cystitis. A third alternative, largely used in Great Britain, is to treat with cyclophosphamide for 3 months and then to switch to oral azathioprine [84]. The use of prednisone alone for the treatment of ANCA SVV is no longer justified on the basis of a lower remission rate and a 3-fold higher incidence of relapse [78].

The optimal duration of alkylating therapy is still very much a matter of controversy. Some investigators suggest 6 months, provided the patient is in clinical remission, while others recommend a full year of therapy. If the patient no longer has any evidence of microscopic hematuria, mild to moderate amounts of proteinuria (less than 2 g/24 hours), and no extrarenal manifestations of disease at 6 months, the treating physician may comfortably cease alkylating therapy. Conversely, additional therapy is warranted if the patient has persistent signs of ongoing glomerulonephritis with red cells and red cell casts, or if there are signs and symptoms of extrarenal manifestations of disease (especially in the upper respiratory tract, the nose, and subglottic region). Alkylating therapy should be continued, either intravenously on a monthly basis or with daily oral cyclophosphamide. Continuation of oral azathioprine is considered a matter of course in Great Britain.

For some individuals, the usual induction therapy is not successful. These individuals are primarily those who have massive pulmonary hemorrhage. In our own experience, the institution of plasma exchange, in addition to pulse methylprednisolone, is warranted in these individuals. The consequence of early and aggressive institution of plasma exchange has substantially diminished the mortality associated with massive pulmonary hemorrhage; the plasma exchange is given on a daily basis for the first week and then every other day for a total of 14 days. The role of pooled intravenous gammaglobulin for this disease is largely anecdotal, although some investigators feel that this drug enhances early induction therapy by diminishing pulmonary symptoms.

The conventional therapy for treatment of relapse is to reinstitute the same form of therapy used in the initial induction and remission protocol. Whether intravenous methylprednisolone is necessary again depends upon the total amount of corticosteroid that has been administered to the patient over the course of the disease, as well as the severity of the relapse. Six months of cyclophosphamide, either intravenously or orally, is again recommended. If the patient is in remission, the question becomes whether long-term immunosuppressive therapy is indicated. Some investigators would suggest that no additional therapy should be used, while others suggest that low-dose prednisone and azathioprine should be maintained for the long term.

With the use of alkylating agents of any kind, remission rates of between 70% and

85% have been noted. Individuals who relapse will either do so immediately after therapy is stopped or within a mean of 13 months. The value of ANCA titers in predicting relapse is a matter of controversy, although most investigators would suggest that they are, at best, adjunctive to clinical history and physical and laboratory examination of the patient. If a patient has an ANCA titer that becomes negative and then suddenly becomes positive again at sufficient titer, it is wise to follow those patients vigilantly to detect early relapse. The treatment of frequent relapse can be particularly challenging in patients with nasal or subglottic vasculitis and destruction. In fact, it may be impossible to withdraw patients with this phenotype from long-term therapy.

Patients who require dialysis at the onset of their disease may or may not respond to induction treatment. Whether plasma exchange or pulse methylprednisolone improves the chances of a dialysis-free interval is a matter of conjecture. In our own experience, only half of the patients who began dialysis responded to treatment. When response did occur, dialysis-free intervals lasted from 3 months to 3.5 years. Half of the patients did not respond to any form of therapy and remained dialysis dependent. There were untoward complications of the treatment regimen, including death.

Alternative Treatment Strategies

There has been substantial interest in alternative therapy to prevent the recurrence of vasculitis. This has been most demonstrated with the use of trimethoprim-sulfamethoxazole combinations. In a study by Stegeman et al. [95], the prophylactic use of cotrimoxazole resulted in a significant decrease in the relapse rate of patients with ANCA SVV. Close inspection of the data reveals that the significant diminution of the vasculitis relapse rate was entirely attributable to the amelioration of the nasal and upper respiratory tract relapse. These data would support those derived from DeRemee et al. [107] who suggest that trimethoprim-sulfamethoxazole combinations are the best forms of therapy for local disease of the head and neck. At this time, there is no apparent benefit associated with the use of these antibiotics for disease outside of this area.

Methotrexate has been evaluated in the treatment of SVV as well. Its use is primarily for individuals without substantial renal involvement, because the risk of mucositis is greatly increased when the creatinine is above 2 mg/dL [93]. Preliminary data suggest that methotrexate might be a useful agent to prevent relapse of SVV outside the kidney. Further studies are necessary in this regard.

On an experimental basis, mycophenolate mofetil has recently been tried as an alternative therapy to maintain remission and treat relapse. This form of therapy has not undergone extensive evaluation, but may be of specific benefit in lesions of the subglottis.

Renal Transplantation

Currently, the value of ANCA tests should not alter the timing of renal transplantation. In renal transplant recipients, there is a 15 – 20% incidence of relapse in the transplanted kidney or elsewhere. Whether newer immunosuppressive therapy, e.g. mycophenolate mofetyl, decreases the risk of relapse is not known. In patients with relapse, substitution of cyclophosphamide for other immunosuppressive therapy is warranted.

Medium- and Large-vessel Vasculitis

Polyarteritis Nodosa and Takayasu Arteritis

Classic polyarteritis nodosa, by the definitions of the Chapel Hill consensus conference, affects arteries but not other vessels. Therefore, by this definition, patients with polyarteritis nodosa do not have glomerulonephritis. Thus, the renal vascular disease is largely that of aneurysm formation in renal arteries resulting in infarction and/or hemorrhage. In some studies, most patients with polyarteritis nodosa have hepatitis B infection (considered later in this chapter) [47].

Patients with Takayasu arteritis may have disease involvement at the origin of the renal artery, resulting in renal artery occlusion and decline in renal function or, in rare individuals, precipitous infarction of an entire kidney. The most common presentation, however, is that of renal vascular hypertension associated with mild renal insufficiency.

Henoch-Schönlein Purpura (HSP)

HSP is mostly seen in children, although adults may also be affected. The clinical picture includes leukocytoclastic vasculitis of the skin, abdominal pain, arthralgias, arthritis, and glomerulonephritis. The skin lesions are similar to those of other renal-dermal vasculitic syndromes. There are typically crops of macular and palpable purpuric rashes on the lower extremities, buttocks and flanks, as well as urticarial lesions. The rash may be accompanied by constitutional symptoms such as malaise and fever, especially in children. The abdominal symptoms are vomiting, abdominal pain, frequent colic, melena, and hematochezia. Patients may present with arthralgias, and occasionally with frank arthritis of the large joints. The percentage of patients with HSP who develop clinically significant renal disease varies. When renal disease occurs, it is typically noted within days to weeks after the onset of symptoms. Most patients present with microscopic or, at times, macroscopic hematuria with red cell casts. Proteinuria is typically mild, although some patients may have the nephrotic syndrome. While there is usually a correlation between the clinical manifestations of disease (including urinalysis and serum creatinine) and the pathologic findings, the light microscopic features of the disease appear more severe in some individuals.

Pathology

The glomerular picture of HSP is identical to that of IgA nephropathy, with a spectrum of lesions ranging from mild mesangial proliferation to diffuse endocapillary proliferation, with or without crescent formation (see Chapter 7). By immunofluorescence microscopy, there is IgA deposition, as well as complement components such as C3. By electron microscopy, electron-dense deposits are found, almost always in the mesangium. Capillary wall deposits are most common in patients with severe glomerulonephritis.

Skin biopsy typically reveals a leukocytoclastic vasculitis involving postcapillary venules. While this finding is present in other renal-dermal vasculitic syndromes, the presence of IgA deposition in vessels is relatively specific for IgA nephropathy.

No specific laboratory tests are either sensitive or specific markers of HSP.

Clinical Course and Treatment Recommendations

In most children, HSP is a self-limited disorder. This is especially true of the dermal and joint complaints. The gastrointestinal symptoms may be severe and prompt numerous diagnostic studies and even exploratory laparoscopy. Corticosteroids clearly improve the extrarenal manifestations of the disease, including the abdominal pain.

In general, the disease process follows a relapsing and remitting course. The renal lesions vary as well. In individuals with mild mesangial hypercellularity, it is unlikely that any anti-inflammatory or immunosuppressive therapy is appropriate. Because a large number of patients develop spontaneous remission, there is limited enthusiasm for the use of corticosteroids and cyclophosphamide. However, among patients who have acute nephritis or rapidly progressive glomerulonephritis, a substantial proportion (up to 44%) have persistant hypertension or a decline in GFR [45]. Nephrologists tend to use therapies similar to those used in other forms of crescentic glomerulonephritis, including pulse methylprednisolone and cytotoxic drugs.

One of the critical issues concerning HSP is whether the disease process is different in adults than children. In a recent study of 162 patients, including 46 adults, cutaneous lesions were the main clinical presentation in both [11]. Upper respiratory tract infection was more frequent in children, whereas adults had a statistically lower frequency of abdominal pain and fever, and a higher frequency of joint pain. Adults were significantly more severely affected with renal disease and required the use of corticosteroids and/or cytotoxic agents. The outcome was good in both groups, with complete recovery in 94% of the children and in 89% of the adults.

Progressive Systemic Sclerosis (PSS)

Pathology

The histologic findings in the acute renal crisis of PSS are those of a thrombotic microangiopathy. There is glomerular consolidation caused by subendothelial expansion and capillary thrombosis, fibrinoid necrosis of arterioles and edematous intimal expansion in arteries. The chronic changes of PSS resemble chronic hypertensive injury and include fibrotic intimal thickening in arteries and glomerular sclerosis. As a consequence of the vascular changes, there may be signs of chronic tubulointerstitial disease, including interstitial fibrosis, tubular atrophy, and glomerular obsolescence. Some of the tubulointerstitial and glomerular disease may be a consequence of the thrombotic microangiopathy, whereas others are a consequence of hypertension.

The Role of Kidney Biopsy

The kidney biopsy may not provide a definitive diagnosis of PSS, for the findings may be that of hypertensive changes without indicating an underlying thrombotic microangiopathy or acute artery changes. A renal biopsy is indicated in patients with acute renal failure who do not have extrarenal manifestations of PSS, and those for whom the diagnosis is uncertain. A renal biopsy may also be of value in those patients who have an overlap syndrome of PSS and SLE, ANCA SVV, or other forms of mixed connective tissue disease [31, 71]. The clinical dilemma occurs in those patients who have evidence of SLE, dermatomyositis, or a clinically nonspecific manifestation of PSS. In these individuals, a renal biopsy may be most useful.

Laboratory Findings

A positive ANA reponse with a speckled or nucleolar pattern occurs in 70% of scleroderma patients. More specific autoantibodies found in these patients react with DNA topoisomerase I (anti-Scl-70). These more specific antibodies are found in up to 30% of patients with diffuse cutaneous disease. Anticentromere autoantibodies are relatively specific for the CREST syndrome. Antibodies to double-stranded DNA or other nuclear antibodies are uncommon.

Clinical Syndromes

The clinical picture of PSS includes involvement of the skin and subcutaneous tissues with localized or diffuse thickening of the extremities, face, and trunk. This thickening results in hardening of the skin and sclerosis of the fingers (sclerodactyly). Variants of PSS include the CREST syndrome defined by calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasias. In these patients, it is uncommon to have either kidney or other organ system involvement. Similarly, localized forms of scleroderma or limited cutaneous systemic sclerosis are not associated with renal disease.

Raynaud's phenomenon is found in > 90% of PSS patients. Whether Raynaud's phenomenon is associated with PSS or a limited and benign phenomenon can be tested at the bedside by careful examination of the periungual nail beds. The absence or drop-out of capillaries in the nail beds is typical of patients PSS but not in patients with benign Raynaud's phenomenon. Esophageal hypomotility or loss of esophageal sphincter tone is found in 75% of patients with PSS, resulting in gastroesophageal reflux. Small and large bowel hypomotility produces a plethora of symptoms, including malabsorption and bacterial overgrowth. Pulmonary fibrosis occurs in > 50% of patients.

The renal involvement tends to occur early in the course of the disease, usually within 2 – 5 years after the onset. It is possible that the disease process may occur more commonly in the fall and winter.

As many as 75% of all patients with PSS have evidence of renal damage, and 50% have clinically evident renal disease. Some patients have mild proteinuria (typically less than 3 g/day) and varying degrees of mild renal insufficiency and hypertension. Scleroderma renal crisis, characterized by the relatively sudden onset of hypertension and acute onset of renal disease in a patient with no prior evidence of renal injury, occurs in 10 – 15% of cases. In the series from Black et al. [10], severe sclerodermal renal disease occurred in approximately 12% of those patients who had diffuse cutaneous scleroderma, but only 1.6% of those with limited cutaneous scleroderma. The incidence was increased in blacks (21% compared to 7% in whites), and the concomitant use of high-dose corticosteroids and perhaps cyclosporine or tacrolimus (FK 506) accelerated the disease process. Considering the nonspecific nature of these predictive factors, prudence dictates close monitoring of patients with PSS with repetitive measurements of blood pressure, serum creatinine concentrations and urinalyses.

Treatment Recommendations

The pathogenesis of scleroderma renal crisis remains controversial. It is possible that the crisis is analogous to a Raynaud's phenomenon: severe and persistent vasospasm may lead to overelaboration of renin and angiotensin II, resulting in, or at least perpetu-

ating, vasoconstriction. ACE inhibitors are the agents of choice, resulting in improvement in hypertension in up to 90% of patients. While most treatment studies rely on captopril, it is likely that other ACE inhibitors have a similar affect. It is not known whether Ang II receptor antagonists are equally effective. With blood pressure control, there may be reversal of renal insufficiency, diminution of proteinuria, and amelioration of the extrarenal manifestations of systemic sclerosis, including improvement in Raynaud's phenomenon and even improvement of the sclerodermatous skin changes.

In a report reviewing the course of 108 patients with scleroderma renal crisis [108], the 1-year survival before the introduction of treatment with ACE inhibitors was 18%, improving to 76% with these agents. Nonetheless, long-term data indicate that renal failure or death still occurred in half of those patients treated with ACE inhibitors. A significant number of patients with scleroderma renal crisis require renal replacement therapy. These patients may pose substantial difficulties with respect to vascular access, perhaps as a consequence of the hardening of the skin overlying the vascular access and the vasoconstrictive propensity of larger arteries. Peritoneal dialysis may be complicated by fibrosis of the peritoneal membrane altering peritoneal clearance. There are very few reports PSS of transplantation in patients PSS.

Other Rheumatologic Diseases that Affect the Kidney

Patients with rheumatoid arthritis may have several forms of renal injury, including amyloidosis as a complication of long-standing, severe rheumatoid arthritis. These patients, as well as those with seronegative arthropathies, can have proliferative glomerulonephritides, either associated with pauci-immune glomerulonephritis or IgA nephropathy. Patients who are HLA-B27 positive with ankylosing spondylitis or Reiter's syndrome usually have an IgA nephropathy [62].

Relapsing polychondritis is an unusual condition associated with ANCA SVV and a pauci-immune necrotizing and crescentic glomerulonephritis, although other proliferative glomerular lesions have been described.

Patients with Sjögren's syndrome and sarcoidosis typically have a renal presentation of an interstitial nephritis associated with interstitial fibrosis. In both of these circumstances, corticosteroid therapy may have a salutary effect, especially in sarcoidosis where substantial response to glucocorticoids may occur.

Dysproteinemias

There are several dysproteinemias or paraproteinemias with deposition of abnormal proteins in the kidney. These include amyloidosis, light chain nephropathy, cast nephropathy, amyloid (AL and AA), fibrillary glomerulonephritis and immunotactoid glomerulonephropathy, and Waldenström's macroglobulinemia (Table 7). The dysproteinemias, especially light chain-related diseases that cause tubulointerstitial lesions including Fanconi's syndrome or tubular interstitial nephritis, are described in Chapter 8.

Pathology

Many dysproteinemias cause distortions of the glomerular architecture by deposition of the abnormal proteins in distinctive patterns

Table 7. Types of Glomerular Extracellular Fibrillar and Microtubular Structures

Disease	Approximate Diameter and Usual Range (nm)	Most Common Composition
AL or AA amyloidosis	10 (8 – 15)	Light chains or AA protein
Fibrillary glomerulonephritis	20 (15 – 30)	Oligoclonal immunoglobulin
Cryoglobulinemia	30 (25 – 35)	Cryoglobulins
Immunotactoid glomerulopathy	40 (20 – 50)	Monoclonal immunoglobulin

(Table 7). By light microscopy there often is an increase in acidophilic material in the glomeruli. Amyloid is characterized histologically by fluffy pale acidophilic deposits with specific staining properties by Congo red (i.e., apple-green birefringence when viewed with polarized light). These deposits appear as masses of thin nonbranching fibrils by electron microscopy. Amyloid deposits may also be found in small vessels, including arterioles and arteries, and along tubular basement membranes. Primary amyloid (AL) can be differentiated from secondary (AA) amyloid on the basis of immunofluorescent staining of the amyloid deposits with anti-AA protein antibody or antibodies to lambda or kappa light chains.

Light chain deposition disease is characterized histologically by nodular glomerulosclerosis that is identical to diabetic glomerulosclerosis. By electron microscopy, glomerular and tubular basement membranes are thickened by finely granular material, rather than by fibrils like those seen with amyloidosis. Unlike amyloid, the deposits of light chain deposition disease do not stain with Congo red stain. In renal biopsy specimens, approximately 80% of AL amyloid is composed of lambda light chains, whereas approximately 80% of light chain deposition disease is caused by kappa light chains.

Clinical Features, Course, and Therapy

Light chain deposition disease and primary amyloidosis may have similar clinical presentations. In amyloidosis, proteinuria and renal insufficiency are the major renal manifestations of disease. Proteinuria ranges from asymptomatic, non-nephrotic-range to severe, resulting in morbid edema, hypercholesterolemia, and marked hypoalbuminemia. Patients with amyloid frequently have disease in organs other than the kidney, especially the heart, liver, skin, gastrointestinal tract, and synovium. In most patients, multiorgan system involvement is present, with 50% of patients having renal disease and ≥ 40% having cardiac amyloid deposits. In an individual with carpal tunnel syndrome and nephrotic syndrome, the diagnosis of amyloid must be considered, since 25% of patients with primary amyloidosis have carpal tunnel syndrome.

The renal manifestation of light chain deposition disease is nephrotic syndrome and can appear very similar to AL amyloidosis. Both disorders affect the heart, liver, and nerves. AL amyloid more frequently affects the gastrointestinal tract and the lungs, while light chain deposition disease rarely affects those organs. Patients with light chain deposition

Table 8. Causes of Secondary Amyloidosis

Chronic infections
– Osteomyelitis
– Tuberculosis
– Leprosy
– Syphilis
– Xanthogranulomatous pyelonephritis
– Others

Chronic inflammatory disorders
– Rheumatoid arthritis
– Juvenile polyarthritis
– Inflammatory bowel disease
– Ankylosing spondylitis
– Sjögren's
– Bechet's syndrome
– Wipple's disease
– Others

Neoplastic disorders
– Multiple myeloma
– Hodgkin's
– Renal cell carcinoma
– Waldenström's macroglobulinemia
– Others

Inherited Disorders
– Glycogen storage disease
– Familial Mediterranean fever
– Others

disease have a higher plasma creatinine concentration at the time of biopsy and less proteinuria than those patients with primary amyloidosis. In our own studies [51], the plasma creatinine concentration was 2.4 mg/dL in the light chain deposition disease patients, whereas the patients with amyloidosis had a serum creatinine of 5.1 mg/dL. In contrast, patients with light chain deposition disease had a protein excretion rate of 3.7 g/24 hours, and patients with amyloidosis had 6.9 g/day.

The diagnosis of amyloidosis requires the presence of amyloid deposits in tissue. While kidney and liver biopsy are positive in 90 – 95% of cases, abdominal fat pad aspiration is positive in 60 – 90% of cases, bone marrow biopsy in up to 50% of cases, and rectal biopsy in 50 – 80% of patients. Most recently, an alternative to tissue biopsy has been suggested by the use of serum amyloid P component scintigraphy. This test is performed by the intravenous injection of technetium-labeled serum amyloid P component [101]. Scintigraphy has a sensitivity of nearly 100% with uptake in the spleen, kidney, and adrenal. Unfortunately, this test is not widely available, and substantial concern exists that the serum amyloid P protein obtained from numerous blood donors may be contaminated by infectious particles.

A clinical distinction between primary and secondary amyloidosis is based on the presence of systemic disease, especially inflammatory disease associated with secondary amyloidosis (Table 8).

Treatment Recommendations

Unfortunately, patients with primary amyloidosis have a dismal long-term prognosis with a five-year survival rate of <20%. Patients die either of malnutrition or congestive heart failure. While there are occasional responses to a combination of colchicine, prednisone, and melfalan, most patients do not appear to respond to these forms of therapy. In the largest study to date, 220 patients with biopsy-proven amyloidosis were randomly assigned to three different groups: colchicine alone, melfalan and prednisone, or melfalan, prednisone and colchicine. Patients were stratified according to whether they had renal disease, cardiac disease, or peripheral neuropathy. The median survival was only 8.5 months in the colchicine group, 18 months in those assigned to melfalan and prednisone, and 17 months in those assigned to melfalan, prednisone, and colchicine. In this important

study, the overall length of survival was 50 months among those who had a reduction in serum or urine monoclonal protein by 12-months, and 15% of patients survived for ≥ 5 years. This study concludes that treatment with melfalan and prednisone results in prolonged survival and a response to treatment as compared with colchicine alone, and forms the basis of current treatment recommendations. It is important to note that the use of melfalan is associated with melfalan-induced acute myelogenous leukemia (AML) and pancytopenia in about 6 – 20% of patients, depending on the duration of treatment and apparent response of the amyloid [66].

At the cutting edge of treatment, autologous bone marrow transplantation with stem cell rescue or stem cell rescue after ablative chemotherapy has recently been tried in a small number of patients. The relative success of this approach is not certain.

Therapy for secondary amyloidosis is aimed at the treatment of the underlying disorder except in familial Mediterranean fever, where colchicine is most useful in decreasing the severity of the attacks of serositis and arthritis [9]. Colchicine decreases, or at least slows, the accumulation of deposits in the kidney. The symptoms of familial Mediterranean fever are those of episodic attacks of serositis and fever. The use of colchicine in dosages of 1 – 3 mg/day has resulted in substantial diminution in the number of attacks in three-quarters of patients studied.

Other Paraproteinemias

There are several glomerular diseases due to nonamyloid fibrillar deposits. These lesions include fibrillary glomerulonephritis, immunotactoid nephropathy, and fibronectin glomerulopathy. Fibrillary glomerulonephritis is characterized on light microscopy by capillary wall thickening, mesangial matrix expansion, and varying degrees of hypercellularity and inflammation. The fibrils are larger than those of amyloid, but are smaller than those of immunotactoid glomerulonephropathy (Table 7). The deposits of fibrillary glomerulonephritis usually stain intensely for IgG (usually predominantly IgG4) and C3 [60].

Fibrillary glomerulonephrosis is found primarily in Caucasians, with a slightly increased female predominance. The clinical course of all of these forms of fibrillar deposition is largely that of nephrosis, although some patients have hematuria and hypertension as well. Half of all patients develop ESRD despite various forms of experimental therapy. Currently, it is not clear that any form of therapy is of benefit. In fact, most patients do not respond to either prednisone or cyclophosphamide. After 24 months of follow-up, there is only 48% renal survival [60].

Immunotactoid glomerulopathy is a different disorder in which the fibrils are larger and have a microtubular organization. Patients with immunotactoid glomerulopathy are more likely to have a circulating monoclonal immunoglobulin than patients with fibrillary glomerulonephritis. Immunotactoid deposits resemble those of cryoglobulinemia, which usually contain a monoclonal rheumatoid factor component.

The most recently described nonamyloid fibrillar deposition disease is fibronectin glomerulopathy. This extremely rare disease is characterized by massive amounts of fibronectin deposited in the mesangium. These deposits do not stain with Congo red. By electron microscopy, the fibrils are approximately 12 nm in diameter and are composed of fibronectin instead of immunoglobulin.

Paraneoplastic Nephropathies

The concept of paraneoplastic nephropathy is not new. The first report of a nephrotic syndrome associated with Hodgkin's disease dates back to 1939 [79]. In 1996, Lee et al. reported on a series of adults over the age of 40 with nephrotic syndrome [69]. In that cohort of patients, 11% developed neoplasms, all carcinomas. This corresponded to an incidence ten times greater than the age-matched actuarial rate. Interestingly, the renal disease antedated diagnosis of cancer in two-thirds of patients.

The prevalence of paraneoplastic nephropathy among patients with cancer is probably below 0.1% [3]. Conversely, the prevalence of cancers among older patients with glomerulonephritis may be quite high. For example, as many as 20% of patients 60 years and older with membranous nephropathy may have a concurrent cancer. Based on these findings, the search for occult malignancy is recommended in all elderly patients presenting with a glomerular disease.

The spectrum of glomerular diseases associated with concurrent cancers is wide. The most commonly reported nephropathies include membranous glomerulonephritis, minimal change disease, membranoproliferative glomerulonephritis, crescentic and necrotizing glomerulonephritis with or without a rapidly progressive glomerulonephritic syndrome, IgA nephropathy, and focal segmental glomerulosclerosis (FSGS).

Certain nephropathies tend to be associated with specific neoplasms. Membranous glomerulopathy accounts for about 30% of nephrotic syndrome in adults. Whereas it usually presents with proteinuria, as many as 40% of patients in this patient population may not have the nephrotic syndrome. There is a strong association of membranous nephropathy with epithelial cancers, especially those of bronchial or digestive tract origin. In fact, membranous nephropathy has been said to account for 60% to 70% of glomerular involvement in patients with these types of cancer. Conversely, the prevalence of membranous nephropathy among patients with nephrotic syndrome and hematologic cancers is only about 1%.

The characteristic histologic findings of classic or idiopathic membranous nephropathy is characterized by subepithelial immune complex deposits as seen by electron microscopy, however in cases of membranous nephropathy secondary to systemic disease such as SLE or neoplasms, one may find mesangial and/or subendothelial immune complex deposits in addition to the subepithelial deposits. These findings may be a clue for the presence of a secondary membranous nephropathy and should prompt the treating physician to search for an occult malignancy.

Minimal change disease (MCD) accounts for about 25% of nephrotic syndromes in the adult. In adult patients, especially the elderly, there is a higher incidence of hypertension and ARF than is seen in childhood disease. About 15 – 20% of adults may also present with microscopic hematuria. Minimal change disease is strongly associated with Hodgkin's lymphoma. Although the incidence of minimal change disease among patients with Hodgkin's is quite low, accounting for only 0.4% (7/1700 cases), MCD is, conversely, the most common finding in patients with Hodgkin's lymphoma and the nephrotic syndrome. The course of the nephrotic syndrome with MCD has been reported to parallel that of the lymphoma with treatment. The nephrotic syndrome and proteinuria may disappear when the Hodgkin's lymphoma goes into remission. There have also been reports of re-

current proteinuria heralding the recurrence of the lymphoma. MCD has also been reported with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and carcinomas.

Membranoproliferative glomerulonephritis (MPGN) may present as the nephrotic syndrome but may also present as an acute nephritic syndrome with renal failure, microhematuria, and hypertension. It is usually associated with low levels of C3, circulating C3 nephritic factor and circulating immune complexes. It may be the most common cause of nephrotic syndrome in patients with chronic lymphocytic leukemia. MPGN is also pathogenetically associated with essential mixed cryoglobulinemia. Whereas greater than 90% of patients with essential mixed cryoglobulinemia have been reported to be infected with the hepatitis C virus, in those patients who are HCV negative, the cryoglobulins have been suggested to be the result of a monoclonal expansion of B cells producing them and IgM rheumatoid factor.

IgA nephropathy presents in patients between the ages of 10 and 30 years of age in 65% of cases, although it may occur in the elderly population. It usually presents with microscopic hematuria, but may also present with frank proteinuria, hypertension, renal failure and even macroscopic hematuria with tea-colored urine. In one series, 6/66 patients greater than 60 years old with IgA nephropathy were found to have a concomitant cancer, whereas 0/158 patients younger than 60 years old had a cancer. IgA nephropathy was also reported in association with bronchogenic, head and neck, and pancreatic carcinomas.

In a compendium of all glomerular diseases associated with non-Hodgkin's lymphoma, Harper and Adu found that the most common nephropathy associated with B cell non-Hodgkin's lymphoma was focal segmental necrotizing glomerulonephritis (FSNG) [50]. This diagnosis accounted for 12/23 patients with glomerulonephritis and non-Hodgkin's lymphoma. The second most common diagnosis, accounting for 7/23 patients, was MPGN. Interestingly, 6/12 patients with FSNG had no evidence of immune complex deposits by indirect immunofluorscence microscopy. Those reports make no mention of ANCA testing or ANCA positivity. The pauci-immune histology reported raises the possibility that this could be associated with the presence of circulating antineutrophil cytoplasmic autoantibodies. In our experience in a cohort of 206 patients with ANCA SVV and glomerulonephritis, 11 patients developed 12 cancers. Four patients had prostate cancer, 3 colon cancers, and one each stomach, lung, bladder, and skin cancer. One patient had an unknown primary cancer site. Of these 11 patients, 5 were diagnosed with cancer either at presentation with their ANCA SVV or within 3 months thereafter. In these patients, it is unlikely that the development or the rapid growth of the cancer would have been secondary to immunosuppression or the use of cytotoxic drugs. In fact, 2 of these patients never received any cytotoxic drugs, and one patient received cytotoxic drugs for less than 4 weeks.

Kidney Abnormalities Associated with Liver Disease

The kidney is affected in a number of ways once there is liver damage, including derangement of salt and water balance, acute azotemia (especially in the hepatorenal syndrome), and

in association with several glomerular diseases (Table 9). It is beyond the scope of this review to consider the alterations of salt and water disturbances in liver disease or the causes of acute renal insufficiency. Rather, this chapter will focus on the viral hepatitides and the association of IgA glomerulopathy in cirrhosis.

Table 9. The Kidney in Liver Disease

- Sodiumretention
- Water retention
- Acute renal insufficiency
  - Prerenal azotemia
  - Acute tubular necrosis
  - Hepatorenal syndrome
- Viral hepatitis (Hepatitis B, Hepatitis C)
- Cirrhosis
  - Sclerosing glomerulonephritis
  - IgA glomerulonephritis

Hepatitis B

Hepatitis B causes several glomerular syndromes including serum sickness, membranous nephropathy, MPGN, and polyarteritis nodosa. Serum sickness is found in up to 25% of patients with hepatitis B, with associated arthralgias and arthritis, purpura, fever, and transient renal disease.

Membranous nephropathy has long been associated with hepatitis B, especially in Asia and Australia, where the majority of children with membranous nephropathy have hepatitis B. The proof that viral infection has a pathogenetic role in glomerular disease has been demonstrated in a number of ways. The most specific evidence is the immune complex deposits in membranous nephropathy containing hepatitis B antigen and especially the Hbe antigen [63]. In addition, both hepatitis B viral DNA and RNA have been observed in glomerular and tubular cells in patients with renal disease. Fortunately, in children with hepatitis B, spontaneous remission almost always accompanies the disappearance of hepatitis Be antigenemia and conversion to a positive hepatitis Be antibody state, contraindicating treatment with immunosuppressive drugs so as not to either stimulate viral replication or alter the development of an antibody state.

Whether there is a role for alpha-interferon therapy in hepatitis B and other types of glomerular injury is controversial. Conjeevaram et al. treated 15 chronic hepatitis B glomerulonephritis patients with alpha-interferon [23]. Of these individuals, half had a long-term serological response with loss of the serum hepatitis B antigen and hepatitis B viral DNA. Seven of 8 patients had a gradual improvement in proteinuria, although their liver disease improved more quickly. All 8 had membranous glomerulonephritis. Interestingly, of the other 7 patients, 4 had MPGN. This study suggests that the interferon-α may have an ameliorative role in the treatment of hepatitis B-associated membranous nephropathy in adults.

Polyarteritis nodosa has been associated with hepatitis B [47]. The symptoms of the disease may vary from subtle weight loss and malaise to sudden perforation of the abdominal viscus and renal infarction. The spectrum of injury includes mononeuritis multiplex, abdominal pain from ischemic injury to the bowel wall, central nervous system infarctions including central retinal arteritis, coronary arteritis resulting in myocardial infarctions, deep nodular lesions in the skin, and arterial damage in other vascular beds with

associated tissue destruction [47]. The treatment of hepatitis B-related polyarteritis nodosa is best described in a recent study by Guillevin. Of 41 patients with hepatitis B-associated polyarteritis nodosa, 35 were treated with the antiviral agent vidarabine, and 6 patients were treated with interferon α and plasma exchange. Fifty two percent of patients converted to hepatitis B antibody and 24% also seroconverted to anti-hepatitis B surface antibody. In fact, half of the patients no longer had serologic evidence of hepatitis B viral disease at all. Eight patients died.

The treatment strategy at present is short-term steroid therapy, antiviral agents, and plasma exchange. The use of corticosteroids and cyclophosphamide, which may or may not facilitate viral replication, is not indicated.

Hepatitis C (HCV) -related Glomerulonephritis

Cryoglobulins are composed of different types of immunoglobulins, which may be separated into 3 types. Whereas type I cryoglobulins are characterized by the presence of monoclonal antibodies, usually IgM, type II and type III are mixtures of monoclonal and polyclonal, or polyclonal with polyclonal immunoglobulins, respectively. In type II mixed cryoglobulins, the monoclonal component is usually an IgM with a kappa light chain. The polyclonal component is usually an IgG, with either type of light chains [2]. A growing number of reports have linked HCD infection and type II cryoglobulin [16, 33, 81].

Cryoglobulins are detectable in up to 30% of patients with HCV, but the clinical syndrome of mixed cryoglobulinemia occurs only in 1 – 2% of patients with HCV infection. Misiani et al. studied the association between HCV infection and cryoglobulinemia in 51 patients, using as controls 45 patients with non-cryoglobulinemic glomerulonephritis [74]. The authors looked for the presence of HCV by a number of different techniques, including a c100 ELISA and a c22/c200 ELISA, a recombinant immunoblot assay (4 RIBA), and a serum HCV RNA by PCR. Depending on the assay used, up to 98% of patients with type II cryoglobulinemia had evidence of HCV infection compared to only 2% in the control group. In addition, the study of the cryoglobulin precipitate revealed detectable anti-HCV activity in the cryoglobulin precipitate from 94% of patients after the use of dithiothreitol, a substance that destroys the IgM antibodies with rheumatoid factor activity. Similarly, Agnello et al. demonstrated that the concentrations of HCV, RNA, and anti-HCV antibody, but not antibodies to EBV or rubella, were much higher in the cryoglobulin precipitate than in the corresponding serum [1].The high prevalence of HCV infection and type II cryoglobulinemia, as well as the demonstration of anti-HCV antibodies and HCV RNA in the cryoglobulin precipitate, provides compelling evidence of an association between HCV infection and the development of type II cryoglobulinemia.

The mechanism by which HCV infection might lead to the development of type II cryoglobulinemia is unclear. The recent finding that peripheral blood leukocytes, especially B cells, can be the site of extrahepatic HCV replication has led to the postulation that direct active viral replication in B cells induces type III mixed cryoglobulins by triggering the activation of B cells to hyperproduce polyclonal IgM rheumatoid factors in a subgroup of patients with chronic infection. Some other uncharacterized event might induce the abnormal proliferation of a single clone, leading to the production of a monoclonal IgM rheumatoid factor and type II mixed cryoglobulinemia.

Pathology

The most common renal lesion in patients with type II mixed cryoglobulinemia is type I MPGN. Pathologic characteristics include endocapillary hypercellularity due to proliferation of mesangial and endothelial cells, and infiltration of monocytes and T lymphocytes. There are typically large amorphous eosinophilic, PAS-positive, Congo red-negative deposits that may fill the capillary lumina ("hyaline thrombi"). The basement membrane is typically thickened with a "double contour" appearance. A few patients have fibrinoid necrosis of the walls of arterioles and venules. Electron microscopy may reveal subendothelial electron dense deposits consisting of a microtubular structure of hollow fibers, 100 to 1000 nm long. By immunofluorescence microscopy, there is granular-to band-like staining of the vessel walls for IgM, IgG, and complement C3 (144). Some patients exhibit intense staining of large deposits that fill the capillary lumen.

Clinical Manifestations

Type II mixed cryoglobulinemia is most often diagnosed in the fifth and sixth decade of life, often many years after the first symptoms appear. Cryoglobulinemic vasculitis is often characterized by purpura, weakness, arthralgias, arthritic vasculitis, neuropathy and proliferative glomerulonephritis. Renal involvement occurs in 8 – 58% of patients and is more common in women with mixed cryoglobulinemia. Manifestations of renal involvement typically appear many years after the first symptoms of cryoglobulinemic vasculitis develop. The renal disease may occasionally appear concomitantly with the extrarenal manifestations, but rarely before. The most frequent renal findings are isolated proteinuria and microscopic hematuria with moderate chronic renal insufficiency. Twenty to 30% of patients may present with an acute nephritic syndrome with ARF, severe proteinuria, hematuria and hypertension. Twenty percent of patients may present with a nephrotic syndrome.

Clinical Course and Prognosis

The clinical course of type I MPGN associated with HCV varies. Ten to 15% of patients attain complete remission, even when presenting with an acute nephritis, while 30% of patients follow an indolent course that does not progress to ESRD despite the persistence of abnormal urinary sediment and chronic renal insufficiency and 20% of patients may have recurrent episodes of acute nephritis that may go into remission either spontaneously or in response to high-dose corticosteroids and/or plasmapheresis. The latter course usually leads to chronic renal insufficiency. According to the data of D'Amico et al., only about 15% of patients progress to ESRD over a mean period of 10 years [41]. These authors, however, report a high mortality rate over the same period of time secondary to extrarenal disease. Based on a cohort of 105 patients diagnosed over 25 years [98] and followed up for a median of 72 months post-biopsy, the 10-year probability of survival without ESRD was 49%. The major causes of death in that group were due to cardiovascular disease, infection, liver failure, and neoplasia. The main risk factors were age > 50, vascular purpura, splenomegaly, cryocrit level > 10% and C3 plasma levels < 54 mg/dL. As with other glomerulonephritides, a serum creatinine > 1.5 mg/dL was an important risk factor for chronic renal failure or death (relative risk of 1.25, 95% confidence interval of 1.11).

Treatment Recommendations

The recognition of an association between HCV infection and type I MGPN has led to great interest in the treatment of this glomerular disease with antiviral agents. While a large body of data has accumulated over the last several years concerning the treatment of HCV infection, most knowledge is derived from the treatment of hepatic disease. Several subtypes of interferon alpha have been employed. One of the first reports, by Misiani et al., was a randomized study of the use of interferon alpha in the treatment of patients with HCV-related mixed cryoglobulinemia [75]. Patients were treated thrice weekly for 24 weeks versus symptomatic therapy in the control group. Treatment with interferon p–α resulted in improvement in cutaneous vasculitis, cryocrit, and serum creatinine, and a decrease in HCV RNA. However, the viremia and cryoglobulinemia recurred in all patients after discontinuation of interferon alpha. Carithers et al. performed a meta-analysis of interferon alpha 2b trials [19]. The results are expressed as biochemical response (correction of alanine amino-transferase, ALT) or serologic response (decrease in or disappearance of HCV virus titers). Response is defined as either "end of treatment response" or "sustained response", referring to the result six months after discontinuation of treatment. The authors report a biochemical end of treatment response of 47% and 29% for virologic response. The sustained response dramatically drops to 23% and 8%, respectively. Treatment for prolonged periods (12 to 24 months versus 6 months) or with high-dose interferon alpha might lead to a very modest improvement in these results. Most patients experienced mild to severe influenza-like symptoms.

The results of the use of interferon alpha alone led to the evaluation of combination therapy including interferon alpha and the nucleoside analog ribavirin [87]. Three randomized placebo-controlled studies comprising more than 150 patients have shown that therapy with Ribavirin alone for 24 – 48 weeks resulted in an improvement ALT levels, but no substantial reduction in HCV RNA levels. ALT levels increased to pretreatment values when therapy was discontinued. However, ribavirin in standard doses combined with interferon alpha in doses of 3 million units, 3 times weekly for 6 months, was found to significantly improve the sustained biochemical and virological response rates compared to interferon alpha alone. No study has yet been reported as to the use of this combination therapy in the treatment of HCV-related mixed cryoglobulinemia or MPGN.

There are currently 2 non-randomized case series on the use of plasmapheresis with or without small doses of corticosteroids in the treatment of acute exacerbation of cryoglobulinemic MPGN [12, 39]. These case series report a beneficial effect of plasmapheresis in the treatment of acute exacerbation of vasculitis. Patients with acute deterioration of renal function seemed to benefit the most, whereas patients with chronic stable renal insufficiency had a less marked benefit from the treatment. Of note is that in 5/9 patients [39] plasma exchange led to sustained remission without clinical relapse when the procedures were reduced in frequency or discontinued.

Cirrhosis

Cirrhosis of the liver is associated with two syndromes. First, in many cirrhotic patients, there is an associated diffuse glomerular sclerotic process that has been called "cirrhotic glomerulosclerosis". By immunofluorescence microscopy, some of these samples

have IgA or IgM deposition. The second, and most common histologic finding is a process indistinguishable from idiopathic IgA nephropathy. In fact, IgA deposition with variable degrees of MPGN is found in 50% of autopsy subjects who have died with alcoholic liver disease. The IgA deposition in this circumstance (clinical course of IgA nephropathy) is reviewed in the previous chapter.

Kidney in Infectious Disease

Acute Post-streptococcal Glomerulonephritis (APSGN)

APSGN is the prototype disease of an acute glomerulonephritis associated with an infectious etiology. The first description linking an acute glomerulonephritis to an infectious etiology dates back to the early 18th century after scarlet fever epidemics in Florence and Vienna. The association was also described in 1838 by Bright, again in association with scarlet fever [109]. Rammelkamp et al. further refined the association of post-streptococcal glomerulonephritis with specific serotypes of Streptococci [85].

APSGN is a disease that affects primarily children, with a peak incidence between ages 2 and 6 years. Children younger than age 2 and adults older than age 40 account for only about 10 – 15% of patients affected with APSGN. The disease is often subclinical and the incidence of subclinical nephritis outnumber that of overt nephritis by a ratio of 4 – 10:1. Males are more likely to have overt nephritis than females.

APSGN may occur as part of an epidemic or as sporadic disease. The clinical syndrome preceding APSGN may be either pharyngitis or a skin infection. In temperate countries, the pharyngitis is more common, whereas impetigo and pyoderma predominate, in the tropics.

Pathology

On light microscopy, APSGN is marked by an acute diffuse proliferative glomerulonephritis. The hypercellularity results both from endogenous mesangial and endothelial cell proliferation, and infiltration of the glomerular tuft by inflammatory cells, especially neutrophils. The early “exudative phase” of disease is characterized by the infiltration of the capillary tuft by neutrophils, eosinophils, lymphocytes, and monocytes. These cells may be present both in the capillary lumen and the mesangium. After 4 – 6 weeks, polymorphonuclear neutrophils (PMN) are usually no longer present and the hypercellularity is mostly residual mesangial hypercellularity.

During the exudative phase and acute disease, there is often occlusion of the capillary lumina. During that time, the capillary walls are thickened by the deposition of large subepithelial immune complexes. In severe cases, crescent formation occurs.

By immunofluorescence microscopy, APSGN is characterized by granular deposits of IgG and C3 distributed in a diffuse granular pattern within the mesangium and along the capillary walls. The IgG usually disappears within a few weeks, leaving a C3-dominant staining that may persist for several months.

By electron microscopy, APSGN is characterized by the deposition of dome-shaped electron-dense deposits (humps) in the

subepithelial zone. These electron-dense deposits are typically seen early in the course of disease, and tend to disappear within two months as the acute glomerulonephritis resolves. Subendothelial, mesangial, and intramembranous deposits also occur in variable amounts and usually persist longer than the subepithelial deposits.

Clinical Manifestations

The glomerulonephritis associated with post-streptococcal disease is typically abrupt in onset. There is a latent period of 7– 14 days after an upper respiratory tract infection, or 14 – 28 days after a pyodermal infection. The most common clinical manifestations of APSGN include symptoms of nephritis, hematuria, hypertension, edema, and oliguria. Anuria and renal insufficiency are uncommon. Patients typically present with mild to moderate hypertension. The hypertension is the most likely cause of headaches that are typically of mild to moderate intensity. However, severe neurological manifestations have been described, including hypertensive encephalopathy with headaches, ocular disturbances, and even stupor, coma, and seizure activity. Excessive intravascular fluid results in pulmonary vascular congestion that may lead to clinical symptoms of dyspnea, orthopnea, and – even in these young individuals – evidence of congestive heart failure (CHF) with pulmonary edema, pleural effusions, and a gallop rhythm. Children typically have systemic symptoms including nausea, vomiting, and abdominal pain with mild fever.

The clinical course in APSGN is usually a self-limited one; resolution of the disease is marked by the institution of a diuretic phase within 1 – 2 weeks after the onset of illness. Associated with the diuresis is amelioration of hypertension and vascular congestion. Interestingly, the hematuria and proteinuria disappear in the vast majority of children within 6 months; in adults, proteinuria may be present in half of patients for more than a year, and one-third may have proteinuria over a longer term. Thus, the long-term prognosis in children is relatively benign, exept in some children with severe crescentic disease, in whom it is likely that evidence of chronic glomerulonephritis persists indefinitely. Some long-term studies of adult patients suggest that complete recovery may take as much as a decade, while some patients may progress to ESRD [17]. Importantly, the episodes of ASPGN that occur in epidemics respond more favorably than do those that occur as sporadic infections.

Treatment Recommendations

No specific treatment is indicated in the care of patients with APSGN. Treatment of hypertension is usually responsive to diuretics as well as other antihypertensive medications, namely calcium channel blockers, or ACE inhibitors. Treatment of acute uremia and advanced renal failure may be indicated, requiring the transient institution of dialysis. No immunosuppressive regimens have been studied and evaluated in the treatment of APSGN. Kobrin and Madaio [65] suggest the use of high-dose corticosteroids for 3 – 5 days only in patients with an rapidly progressive glomerulonephritis (RPGN) and the findings of crescents in > 30% of glomeruli on renal biopsy. These recommendations are not based on clinical trial data. Specific treatment of the streptococcal infection is essential. Both the patient and exposed family members should be treated with penicilline G or erythromycin. It is unclear as to whether treatment of the streptococcal infection prevents the occurrence of nephritis.

Infective Endocarditis, Shunt Nephritis, and Visceral Sepsis

Infective endocarditis, shunt nephritis and visceral sepsis-induced glomerulonephritis are examples of immune-mediated glomerulonephritis. The pathology of each of these syndromes includes a spectrum of proliferative lesions that range from focal proliferative glomerulonephritis, to acute diffuse proliferative glomerulonephritis, to membranoproliferative glomerulonephritis. Evidence of immune deposition is found both by immunofluorescence microscopy and electron microscopy. Granular deposition of immunoglobulins and complement forms along the glomerular capillary wall and in the mesangium. Immunostaining for IgM often is more intense than staining for IgG.

The responsible pathogen in infective endocarditis, shunt nephritis, and visceral sepsis may be different for each condition. Previously, infective endocarditis was largely due to staphylococcal and streptococcal disease, but now includes gram-negative organisms and opportunistic organisms as well, primarily in immunocompromised hosts and those who use intravenous drugs [76]. The same is true for visceral sepsis. Shunt nephritis is associated predominantly with *Staphylococcus sp.*, but also with other organisms, both gram-positive and gram-negative. Interestingly, ventriculoperitoneal shunts are more resistant to infections than are ventriculo atrial shunts.

The clinical manifestations of all of these diseases are very similar, resulting in either microscopic or gross hematuria and proteinuria. While glomerulonephritis is the predominant manifestation, some individuals (up to 25%) present with nephrotic syndrome. Fever, chills, rigors, and leukocytosis are clues to early detection and institution of appropriate antimicrobial agent therapy. The total complement (CH50) and C3 levels are frequently decreased. Cryoglobulins and circulating immune complexes are detected in some individuals. Among patients with visceral sepsis and infective endocarditis, as many as one-third will have dermal manifestations of injury as well, including peripheral emboli in infective endocarditis and purpura.

The treatment of these conditions depends on identification and eradication of the pathogenetic microorganism. In the case of shunt nephritis oraprosthetic heart valve, removal of the foreign body may be required.

Protozoal and Other Parasitic Infections

Nephrotic syndrome is a common consequence of protozoal and parasitic infections. In areas of Africa, especially Uganda, as many as one third of nephrotic children have quartan malaria. Nephrotic syndrome also occurs in other parasitic and protozoal infections, predominantly those associated with Schistosoma mansoni, as noted in Table 1. In patients with typical nephrotic syndrome, glomerular lesions are variable, including membranous glomerulopathy, focal glomerular sclerosis and minimal change glomerulopathy. Fully one third of patients have focal or diffuse proliferative glomerulonephritis, often with a membranoproliferative pattern. A distinctive entity associated with quartan malarial infection is a pattern of glomerular sclerosis with formation of new matrix material in the subendothelial zone, resulting in basement membrane replication and thickening.

Unfortunately, the long-term prognosis of these conditions is poor; there does not appear to be spontaneous remission when nephrotic syndrome is attributable to malaria. Antimalarial drugs do not help, and the effects of

anti-inflammatory and immunosuppressive drugs are unknown. *Schistosoma mansoni* may respond to antiparasitic medications in combination with a variety of anti-inflammatory and immunusuppressive drugs.

Human Immunedeficiency Virus Associated Nephropathy (HIV-AN)

The occurrence of kidney disease in the setting of HIV infection is common and the spectrum of renal disease is very broad. In a retrospective review of 449 patients with acquired immune deficiency syndrome (AIDS) admitted to Bellevue Hospital in New York [103], almost 20% suffered an acute episode of renal insufficiency. In 5% of patients this led to ARF, with a rise in serum creatinines to > 6 mg/dL. In the subset of patients with severe renal failure, the mortality rate was over 50%. In survivors, recovery of renal function was almost complete, except when nephrotoxic antimicrobial drugs were the cause of renal failure.

The etiology underlying ARF in patients with HIV infection or acquired immunodeficiency syndrome (AIDS) is related, directly or indirectly, to sepsis in up to 75% of the cases [88]. Other important causes of ARF are volume depletion with hypotension and acute tubular necrosis precipitated by nephrotoxic drugs, e.g. aminoglycosides, pentamidine, trimethoprim-sulfamethoxazole and NSAIDs. Pathological changes include acute tubular necrosis (ATN), acute interstitial nephritis, and other findings such as nephrocalcinosis, carcinoma, streptococcal abscesses and various glomerular lesions.

HIV-associated nephropathy refers to a specific glomerulonephritis seen in the setting of HIV infection. Its presenting features are those of nephrotic-range proteinuria and renal insufficiency. Most patients present with a full nephrotic syndrome, including edema, hypoalbuminemia and hyperlipidemia. Some patients, however, present with sub-nephrotic-range proteinuria as well as with microscopic hematuria and sterile pyuria.

The course of HIV nephropathy usually progresses rapidly to renal failure. Initially, Rao and Carbone reported a progression to ESRD within a period of about 3 – 4 months among patients with HIV-AN [18, 87]. In the study by Carbone et al., the median length of survival from diagnosis of renal disease to death was determined by the stage of the underlying HIV infection. The longest median survival period (9.7 months) was among asymptomatic patients, as compared to that of patients with AIDS-related complex (ARC) or clinical AIDS, who had median survival periods of 3.6 and 1.9 months, respectively. (It is important to note that these data were derived from the "pre-zidovudine (AZT)" era.) HIV-AN may occur at any stage in the HIV infection, possibly most commonly in asymptomatic HIV-infected patients [18].

From the earliest reports of HIV nephropathy, a geographic discrepancy in the incidence of HIV-AN was noted with a predominance of cases reported from East Coast centers, and a very low prevalence of the disease in San Francisco. This geographic difference in prevalence suggested possible associations with the mode of transmission of the infection, with IV drug use, or with racial differences. It is now apparent that there is a strong racial predominance of African-Americans in HIV-AN that is independent of concomitant intravenous drug use. A study by Bourgoignie et al. also describes a much more severe form of the disease among the black population, with blacks being more likely to have nephrotic-range proteinuria and renal insufficiency [14]. This racial difference is also seen in other glomerular diseases such as idiopathic focal segmental glomerulosclerosis,

hypertension and diabetes. The basis for this predilection of HIV-AN among African-Americans is currently unknown.

The incidence of HIV-AN in autopsy and biopsy-based series has varied, depending on geographic location, criteria for diagnosis and indications for biopsy. Overall the incidence appears to be somewhere between 1 – 10%. In the study by Bourgoignie, no relationship was found between the development of nephropathy and patient age, duration of HIV infection or types of opportunistic infections [14].

Pathology

Pathologically, HIV-AN has features of a collapsing form of FSGS, characterized by focal to global wrinkling, thickening and retraction of the GBM, and expanded mesangial matrix, resulting in obliteration of capillary lumens. There is no associated increase in mesangial cellularity. A characteristic feature of collapsing FSGS associated with HIV-AN is hypertrophy and hyperplasia of the visceral epithelial cells overlying the glomerular tuft. These visceral epithelial cells may also show numerous intracytoplasmic protein resorption droplets. There is interstitial edema, fibrosis, and inflammation with variable degrees of tubular atrophy. There often is focal microcystic dilatation of tubules containing proteinaceous casts.

By indirect immunofluorescence microscopy, some degree of staining for IgM, and C3 (and, less commonly, C1q) is seen in the mesangium and in areas of glomerular sclerosis. There may be staining for IgG, IgA, and albumin within the visceral epithelial cell resorption droplets.

By electron microscopy, one can see collapse of the glomerular tufts with wrinkling and retraction of segments of the GBM. There is extensive foot process effacement of podocytes, as well as microvillus transformation. Over 90% of HIV-AN biopsies reveal numerous tubuloreticular inclusions within endothelial cells. These inclusions consist of 24 nm tubular structures located within the endoplasmic reticulum. These structures (also seen in SLE) are thought to be the result of interferon α activation.

There is some controversy as to whether one aspect of HIV-AN consists of diffuse mesangial hypercellularity. A milder mesangial lesion appears to be more common in children and caucasian patients, and is associated with less severe proteinuria.

Treatment Recommendations

No specific treatment for HIV-AN is currently available. The care of patients with HIV-AN consists of 3 goals: (1) the reduction in proteinuria in an attempt to minimize the nephrotic syndrome, (2) the delay of progression to ESRD, and (3) the provision of renal replacement therapy when ESRD is reached.

– *Minimizing proteinuria.* To date, 3 studies involving small numbers of patients with nephrotic syndrome and HIV infection have documented a reduction in proteinuria resulting from treatment with an ACE inhibitor. This benefit appears to be associated with stabilization in renal function. Overall, the use of ACE inhibitors in HIV-AN seems to be of benefit. However, this intervention is sometimes limited by the development of hyperkalemia, especially in patients concomitantly receiving trimethoprim-sulfamethoxazole.
– *Delay of progression to ESRD.* Two lines of intervention currently available are (a) treatment with antiretroviral drugs, and (b) immunosuppression with high-dose corticosteroids. Several reports involving

series of patients with HIV and the nephrotic syndrome suggest that treatment with AZT decreases the degree of proteinuria and delays the progression of HIV-AN to ESRD.

Some of these studies are case controlled, others are prospective studies compared with historic control subjects [59], and other studies are uncontrolled [67, 73]. It is likely that the effect of AZT may depend, in part, on the stage of histologic progression and the degree of azotemia attained at the time treatment is instituted. It is noteworthy that these were derived in the early days of HIV treatment; at the time when treatment of HIV was almost entirely dependent on the institution of AZT. No new data are currently available on the effect of combination therapy with reverse transcriptase inhibitors or protease inhibitors. Likewise, there are no data concerning the effect of combination therapy on the incidence of HIV nephropathy.

The other line of treatment to delay progression of azotemia to ESRD has been based on immunosuppression, with reports of improvement in renal function and proteinuria in response to high-dose corticosteroids. Most reports are single cases, although a few case series that have included HIV-infected children and adults. Whereas the use of high-dose corticosteroids seems to improve proteinuria and delay the decline of renal function, this treatment appears to be associated with a high incidence of life-threatening infections. Based on these results, it is difficult to recommend the use of high-dose corticosteroids to all patients with HIV-AN.

Renal Replacement Therapy

The issues of renal replacement therapy in HIV-infected patients pertain to (1) long-term survival after reaching ESRD, and (2) the choice of renal replacement therapy modality.

Long-term Survival

Early reports of dismal survival prospects for patients with ESRD has led to reluctance to start replacement therapy in these patients. More recent studies, however, have documented a stratification of the survival rate of patients with HIV infection and ESRD that depends on the stage of their HIV infection. It now appears that patients with HIV infection and ESRD have a survival rate similar to that of stage-matched patients without ESRD. However, the survival of patients on dialysis with AIDS remains poor, with a mean survival of about 3 months, as opposed to about 16 months for patients with ESRD and asymptomatic HIV infection. A recent cross-sectional study [58] assessed the survival of HIV-infected patients requiring dialysis. Of 34 subjects, 29 patients had clinical AIDS. Surprisingly, only 6 patients were receiving an antiretroviral medication (AZT = 5; dideoxyinosine (DDI) = 1). In 68% of cases, AIDS was diagnosed before ESRD; the remaining patients were diagnosed with HIV infection only after initiation of maintenance hemodialysis. In this cohort, the mean duration of ESRD was 57 months, with a range of 4 to 196 months. The mean survival is remarkably improved over the initial reports by Rao [88] and others [57, 80], when the mean survival of AIDS patients on hemodialysis was about 3 months. The authors suggest that the improved survival may be attributed to several factors, including more aggressive institution of dialysis, more aggressive dialysis, improved treatment of opportunistic infection, improved management of uremia including the use of erythropoietin, and perhaps the improvement in anti-retroviral medication. The latter point is not directly supported by

this study, in which only 17% of patients received anti-retroviral medication.

Choice of Modality of Renal Replacement Therapy

There was considerable fear of transmission of HIV infection from patients to staff or other patients in the setting of the use of hemodialysis. This fear has not been substantiated by any reports of patient-to-patient or patient-to-staff transmission of the disease in hemodialysis units in the United States. To date, the cases of patient-to-patient spread of the infection in a dialysis unit in Columbia, South American can be attributed to the reuse of access needles in that country. The same measures taken to prevent spread of the Hepatitis B virus are sufficient to minimize the risk of HIV transmission.

The early interest in the use of peritoneal dialysis in patients infected with the HIV virus stems from the concern to minimize risk of disease transmission to staff and other patients. Whether the rates of peritonitis in this patient population is higher than in control populations remains to be confirmed, as current reports are conflicting. There is no comparison of survival among patients treated with peritoneal dialysis versus hemodialysis.

Emerging Infections

Two viruses of note have emerged that may prove to be important causes of glomerular and tubular interstitial injury. The Hanta virus infection, known to cause hemorrhagic fever with renal involvement, was of substantial consequence during the Korean War. Recently, cases have been described in the United States, primarily causing respiratory distress. The renal lesions in these patients was confined to slight mesangial alterations with tubulointerstitial inflammation and ARF.

The parvovirus B19 has been recently associated with FSGS and especially the collapsing variant of FSS. Whether this association leads to improved understanding of the pathogenesis of this condition remains uncertain.

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The Kidney in Pregnancy

Claudia Peano and Susan Hou

Anatomic Changes in the Kidney during Pregnancy

Anatomical changes occur in the kidney during pregnancy. Renal length is increased by 1 to 1.5 cm [1]. A physiologic dilatation of the ureters gives rise to hydronephrosis, with urinary stasis of up to 300 cc in the ureters, a change which predisposes to urinary tract infection (UTI) [2]. The ureteral dilatation occurs as early as 12 weeks gestation in response to increased estrogen and progesterone as well as increased prostaglandin E_2 (PGE_2), which decreases ureteral peristalsis. Dilatation is later aggravated by the expansion of the uterus, and hydronephrosis may become more marked. The role of obstruction has been raised by the observation that dilatation is more marked after 4 months gestation and at distances greater than 5 – 10 cm above the ureterovesicular junction. The obstructive component of ureteral dilatation is aggravated by upright posture. By the third trimester, hydronephrosis graded as severe on ultrasound may be seen in normal pregnancy [3]. The increase in renal size usually reverses during the first week postpartum, but hydronephrosis may persist for 12 weeks postpartum. Stasis of urine in the dilated collecting system makes timed urine collections difficult, and it is important to verify the adequacy of collection by measuring total creatinine production. Establishing a brisk diuresis before starting a timed urine collection will minimize the likelihood of inaccuracy resulting from urine stasis. Methods of measuring glomerular filtration rate (GFR) that rely on radioisotopes such as iothalamate cannot be used in pregnancy.

Changes in Renal Physiology during Normal Pregnancy

Dramatic changes in renal function occur during pregnancy (Table 1). Renal plasma flow increases to 50 – 70% above normal during the first two trimesters and remains 40% above normal in the third trimester [4]. An increase in GFR begins by the fourth week of gestation, peaks at 150% of normal at 13 weeks, and continues almost until term. There is dilatation of both afferent and efferent arterioles, and increased renal blood flow is the major determinant of GFR. There is little pressure change across the glomerular basement membrane (GBM) [5]. Mean blood urea nitrogen (BUN) is 9 mg/dL and mean serum creatinine is 0.5 mg/dL. Despite an average decrease in serum albumin of 1.5 gm/dL

Table 1. Renal Changes in Normal Pregnancy

Anatomic
- 1 cm ↑ in length
- Dilatation of the collecting system

Physiologic
- 50% ↑ in GFR: normal
- BUN 9 mg/dL, creatinine 0.5mg/dL
- Respiratory alkalosis: normal PCO_2 27 – 32 mm Hg, HCO^-_3 18 – 21 mEq/L
- Decreased serum osmolality: normal 276 – 278 mOsm/L
- Doubling of uric acid clearance: normal 3 – 4 mg/dL
- ↓ Tubular reabsorption of glucose
- 40% ↑ in renal blood flow
- Decreased afferent and efferent arteriolar resistance
- Decreased BP: normal < 125/75 mm Hg 2nd trimester, < 125/85 mm Hg 3rd trimester
- ↑ Renin (8x), angiotensin (4x), aldosterone (10 – 20x)
- ↑ Prostacyclin and thromboxane

(from 4.7 to 3.2 g/dL), a significant decrease in the oncotic gradient across the glomerular basement membrane has not been found in animal models.

Tubular function also changes. The threshold for reabsorption of glucose increases, and glycosuria may occur without hyperglycemia [4]. Amino acid excretion is increased.

Uric acid clearance is increased in pregnancy from 6 – 12 mL/min to 12 – 20 mL/minute [6]. Increased glomerular filtration is the primary cause of increased uric acid clearance, but a role for decreased tubular reabsorption is suggested by an increase in the ratio of urate to inulin clearance. Normal uric acid in pregnancy is 3 – 4 mg/dL, and an increase in serum uric acid is a sensitive indicator of preeclampsia.

Salt and Water

Pregnancy is accompanied by retention of 900 mEq of sodium and 6 – 8 liters of water, of which 4 – 6 L is in the maternal intravascular and interstitial space. Plasma aldosterone begins to increase early in the first trimester and reaches 5 fold elevation by 16 weeks gestation and a 7–10 fold elevation by term. Early in the third trimester, serum aldosterone levels are 7–10 times greater than in the nonpregnant state, with greater elevations in urinary aldosterone [7]. Plasma renin activity (PRA) increases 4 fold early in pregnancy and then plateaus. Angiotensin II (Ang II) levels double early in pregnancy and rise to 3–4 times normal by term. Despite increased serum levels, pregnant women retain sodium and shut off aldosterone secretion in response to exogenous mineralocorticoid administration.

Osmolality

The osmostat is reset such that thirst is experienced at a level 10 mOsm below the nonpregnant normal, and serum sodium is about 5 mEq/L below nonpregnant normal. The set point for ADH release is decreased from a serum osmolality of 285 to 276 – 278 mOsm/L. While ADH is released at a lower serum osmolality, the rate of metabolic breakdown of ADH is increased because of vasopressinase produced in the placenta [8]. A short-lived diabetes insipidus (DI) secondary to excessive placental vasopressinase may occur in the third trimester. The syndrome is classified as neither central nor nephrogenic. It does not respond to ADH but does respond to synthetic desmopressin (DDAVP), which is not broken down by the enzyme [9]. Women with mild central DI suffer a worsen-

ing of their disease during pregnancy because they cannot increase vasopressin production.

Acid-base Metabolism

Pregnancy is accompanied by a chronic respiratory alkalosis caused by increased ventilation in response to progesterone [10]. Normal partial pressure of CO_2 (Pco_2) is 27 – 32 mm Hg, and normal serum bicarbonate is 18 – 21 mEq/L. The urine is usually alkaline. Changes in acid-base status should be kept in mind when evaluating maternal conditions associated with an increase in serum bicarbonate, such as vomiting and diuretic use. Increases in serum bicarbonate to the high 20s or low 30s may reflect critical alkalemia.

Hemodynamic Changes

Diastolic blood pressure decreases by 7 – 10 mm Hg during the first trimester and returns to prepregnancy levels in the third trimester. Changes in systolic blood pressure are less marked because the increase in cardiac output that occurs in normal pregnancy offsets the vasodilatation. The drop in blood pressure in normal pregnancy occurs despite sodium retention and increased levels of renin, angiotensin, and aldosterone. There is resistance to the hypertensive effects of both endogenously- and exogenously-administered angiotensin. The resistance has been attributed to production of prostacyclin by placental endothelial cells as well as other vasodilators, the relative importance of which is an area of intense study.

Hypertensive Disorders of Pregnancy

Hypertension complicates about 2 – 10% of pregnancies in the United States and is the most important cause of maternal morbidity [11]. In a previously normotensive woman, a rise in systolic blood pressure of 30 mm Hg or a rise in diastolic blood pressure of 15 mm Hg on 2 measurements taken 6 hours apart is considered hypertension. Women with a mean arterial pressure > 90 mm Hg in the second trimester have an increased frequency of stillbirth and neonatal death [12].

Classification

Most centers in the United States use the classification for hypertension in pregnancy proposed by the American College of Obstetricians and Gynecologists in 1972 [11]. This classification divides the hypertensive disorders of pregnancy into preeclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension. The latter is a retrospective diagnosis. Hypertension occurs late in pregnancy without proteinuria and resolves postpartum. It may recur in subsequent pregnancies and is predictive of hypertension in later life.

Preeclampsia

Clinical Presentation

Preeclampsia is characterized by the triad of edema, hypertension, and proteinuria occurring after 20 weeks gestation. Risk factors for preeclampsia are listed in Table 2. Preeclampsia and eclampsia may develop post-

Table 2. Risk Factors for Preeclampsia

– Primigravida
– Different father in pregnancy for multigravida
– Diabetes
– Preexisting hypertension
– Renal disease
– Twin gestation
– Hydatidiform mole
– Fetal hydrops
– Family history

Table 3. Signs and Symptoms of Severe Preeclampsia

– Thrombocytopenia
– Microangiopathic hemolytic anemia
– Elevated transaminases
– Disseminated intravascular coagulation (DIC)
– Congestive heart failure (CHF)
– Retinal detachment
– Ascites
– Seizures
– Cortical blindness
– Acute renal failure (ARF)
– Hepatic rupture

partum, with 20% of the severe form of preeclampsia referred to as HELLP syndrome (see below) [13] and 4 – 10% of seizures [14] occurring postpartum.

Although the development of edema is part of the classic description of preeclampsia, clinically it can be difficult to interpret. Eighty percent of pregnant women develop edema during pregnancy, and, paradoxically, edema may be absent in some women with severe preeclampsia. Nonetheless, the first manifestation of preeclampsia is often a rapid weight gain that may precede the development of hypertension and proteinuria. The latter conditions usually appear after weight gain, and preeclampsia is unlikely in their absence. Symptoms of severe preeclampsia include headache, visual disturbances, and right upper quadrant pain. Objective observation of blood pressure or proteinuria is more important than subjective symptoms in making the diagnosis of preeclampsia because 59% of women who progress to eclampsia have no premonitory symptoms [15].

Severe preeclampsia is a multisystem disease (Table 3). The most common abnormalities are microangiopathic hemolytic anemia, elevated liver enzymes, and low platelets, giving rise to the acronym HELLP.

Hemolytic anemia is characterized by schistocytes on peripheral smear. The magnitude of hemolysis may be masked by intravascular volume contraction, which leads to a hematocrit higher than it otherwise would be. The platelet count may drop below 20,000 platelets/mm^3 as a result of platelet activation and consumption. There is consumption of clotting factors even in the absence of changes in prothrombin time (PT) and partial thromboplastin time (PTT). In approximately 20% of instances, frank disseminated intravascular coagulation (DIC) is seen [13]. There is an association of abruptio placentae with the development of DIC.

The liver disease of preeclampsia presents with right upper quadrant pain and elevated bilirubin and transaminases. Preeclampsia is one of a handful of conditions that can result in transaminase levels > 1000 U/L. Pathology is characterized by periportal hemorrhage and deposition of fibrin and fibrinogen in the sinusoids. The most severe manifestation is hepatic rupture, which may result in exsanguination.

GFR is generally decreased in preeclampsia but may remain within the nonpregnant normal range. Severe preeclampsia may give rise to acute renal failure (ARF) with acute tubular

necrosis (ATN) and, rarely, cortical necrosis (see section below on acute renal failure).

Loss of vision has been described in preeclampsia. There are rare reports of retinal detachment [13]. A second uncommon cause of blindness is occipital ischemia, which gives rise to low-density areas on computed tomography (CT) scan and hyperintense lesions on magnetic resonance imaging (MRI) [16]. This occipital blindness is generally reversible.

Ascites occurs in as many as 10% of patients with HELLP syndrome and is associated with a 26% incidence of congestive heart failure (CHF) [17]. Although pulmonary edema may occur in severe preeclampsia, information about hemodynamic changes in preeclampsia is conflicting. There is a marked increase in peripheral resistance and a decrease in intravascular volume, despite sodium retention. Measurements of pulmonary capillary wedge pressure prior to treatment tend to be low normal but are increased in patients with CHF.

The risk of eclampsia in women with preeclampsia depends in great part on prenatal care and management once preeclampsia is present. Eclampsia occurs in < 1% of patients with preeclampsia in some large centers with extensive experience in managing such patients [18]. Severe preeclampsia has been defined by a blood pressure > 160/110, heavy proteinuria, or neurological symptoms, but making the distinction is fraught with hazard. While any one of the manifestations listed above is associated with a high risk of eclampsia, seizures may occur even without proteinuria and when the blood pressure is only mildly elevated or not elevated at all. Douglas and Redman reported on every instance of eclampsia occurring in England in 1992. Nine percent had neither proteinuria nor elevated blood pressure before seizure. Eighty-five percent of seizures occurred within 1 week of a prenatal visit, and only 26% were judged to have had substandard prenatal care. These data suggest that eclampsia cannot be anticipated in some instances. They also suggest that the distinction frequently made between mild and severe preeclampsia may lead to a false sense of security and decreased vigilance in caring for women thought to have mild preeclampsia.

Pathology

The characteristic pathologic changes in the kidney of women with preeclampsia include swelling of the endothelial cells (glomerular endotheliosis), ballooning of capillary loops into the tubule, fibrinogen and lipid in endothelial cells, and occasional foam cells. Rarely, changes similar to focal sclerosis occur, with reversal postpartum. Ischemic changes are less marked than in other organs. The renal pathologic changes resolve 2 – 4 weeks postpartum [19].

Pathophysiology

Preeclampsia is an endothelial cell disorder that may develop in response to placental ischemia resulting from an inadequate trophoblastic migration into the uterine spiral arteries [20]. In normal pregnancy at 16 weeks, the spiral arteries in the uterus lose their musculoelastic tissue and widen to allow an increase in uterine blood flow. In preeclampsia, this loss of musculoskeletal tissue may not occur and there may be necrosis, which gives the spiral arteries the appearance of acute atherosclerosis. Endothelial cell dysfunction leads to increased production of vasoconstrictors and activation of the clotting system. There is increased vascular permeability.

Much of the study of preeclampsia has centered on the pathophysiology of vasoconstriction. The study of the vasoactive substances is confounded by the difficulty of interpreting the effect of changes in the systemic levels of substances that have their greatest effect at the site of production. During normal pregnancy, production of both vasodilator (prostacyclin) and vasoconstrictor (thromboxane) by endothelial cells is increased, and the balance favors the effects of prostacyclin [21]. In preeclampsia, the ratio of thromboxane and prostacyclin production changes, with decreased prostacyclin production and increased thromboxane production, resulting in the predominance of thromboxane effect with diffuse vasoconstriction [21]. Resistance to the pressor effects of angiotensin decreases. In normal pregnancy, endothelin (ET) production by endothelial cells is decreased. Serum levels increase in women with preeclampsia, and because ET is a vasoconstrictor and facilitates platelet aggregation, the possibility that it plays a role in the pathogenesis of preeclampsia has been raised [22]. It is not clear whether increased ET production is a cause or effect of endothelial cell damage.

Decreased endothelial cell production of nitric oxide (NO) has also been suggested as playing a role in the development of preeclampsia. In animal models, blockade of NO production can produce a syndrome similar to preeclampsia [23]. However, serum from preeclamptic women does not change NO production by endothelial cells in vitro. Much of the end-organ disease seen in preeclampsia can be attributed to hypoperfusion resulting from vasoconstriction. Activation of platelets and the intrinsic coagulation pathway also plays a role, producing fibrin deposition and hemorrhage in the liver and generalized bleeding. The pathophysiology of seizures in this disorder is not known. Neurologic manifestations of preeclampsia may be from a combination of mechanisms, including hypoperfusion, bleeding, and cerebral edema. The decreased GFR appears to be caused by a combination of hypoperfusion and capillary occlusion by swollen endothelial cells.

Prevention of Preeclampsia

Numerous attempts have been made to develop a test which will identify women at high risk for the development of preeclampsia. All have been either too invasive for practical use or simply inaccurate. Two interventions have been extensively investigated to determine whether they prevent preeclampsia: low-dose aspirin and calcium supplementation. Despite initial promise, the effects of these two treatments have been disappointing in large trials.

Aspirin Prophylaxis of Preeclampsia

The discovery of the changes in prostacyclin and thromboxane ratios in preeclamptic pregnancies led to efforts to prevent preeclampsia in high-risk women by giving low-dose aspirin. Several small studies demonstrated the usefulness of low-dose aspirin in preventing preeclampsia in women identified as being at high risk [24 – 26]. A placebo-controlled study of 3135 healthy nulliparas found a rate of preeclampsia of 4.6% in the aspirin-treated group and 6.3% in the untreated group ($p = .05$) [27] The Low Dose Aspirin Study in Pregnancy [28] is the largest study of the efficacy of low-dose aspirin in the prevention of preeclampsia. Women ($n = 9364$) at risk for preeclampsia or intrauterine growth retardation (IUGR) were randomized to either low-dose aspirin (60 mg/day) or placebo. This study showed a 12% lower frequency of preeclampsia in the aspirin-treated group, a difference which was not statistically significant. Aspirin administration was associated with a

significant decrease in preterm delivery (19.7% vs. 22.2% for control.) Although the difference in the frequency of preeclampsia was not different for the two groups as a whole, aspirin did reduce the frequency of very early preeclampsia in which the risk of delivery to the fetus is greatest. In both these studies, the effectiveness of aspirin may have been diluted by the inclusion of low-risk women. Three other recent randomized, double-blind, placebo-controlled trials including over 11,000 high-risk women [29 – 31] have not found an effect, even in the subset of women with severe, early-onset preeclampsia. When the data in 2 of these studies were analyzed taking compliance into account, aspirin still had the effect of reducing preeclampsia [32].

The 1993 study found a slight increase in the frequency of abruptio placentae in the aspirin-treated group. The Collaborative Low Dose Aspirin Study in Pregnancy (CLASP) found that the use of low-dose aspirin in pregnancy carries a very low risk of dangerous bleeding, although there was a slight increase in the number of women requiring peripartum transfusions.

Even with the limitations of these studies and the suggested benefit of aspirin in some of the subanalyses, any dramatic benefit from aspirin should have been apparent in studies including >20,000 women. However, women with preexisting renal disease are among those at highest risk for preeclampsia, and the safety of aspirin in these large trials allows defending its use in this subgroup while awaiting the results of subanalyses.

Calcium Supplementation

The results of a prospective, randomized study involving 1194 nulliparous women were reported in 1991. A group receiving 2 g of elemental calcium was found to have a frequency of preeclampsia of 9.8% compared to 14.8% in a placebo-control group [33]. No effect on IUGR or perinatal death was noted. The findings were supported by several other small studies.

The US National Institute of Heath and Human Development has recently completed a prospective, randomized, double-blind, placebo-controlled study that found no difference in the frequency of preeclampsia in 2295 women taking 2 g of calcium daily and 2294 women taking placebo [34]. Nonetheless, pregnant women should routinely receive calcium supplements for bone protection and for calcification of the fetal skeleton.

Treatment of Preeclampsia

The definitive treatment for preeclampsia is delivery of the baby (see Table 4). The manifestations of preeclampsia must be managed until delivery can be effected, or when preeclampsia occurs very early in gestation and is mild enough to warrant an attempt to prolong the pregnancy.

A woman with suspected preeclampsia should be hospitalized because of the difficulty in predicting seizures. A number of pro-

Table 4. Treatment of Preeclampsia

– Admit to hospital
– Anticonvulsants: magnesium sulfate
– Antihypertensive drugs: hydralazine, labetolol
– Indications for delivery
≥ 36 weeks gestation
BP ≥ 160/110 after 24 hours of hospitalization
HELLP syndrome
≥ 3 g of protein in 24 hours
Rising serum creatinine
Headache, blurred vision, scotomata, right upper quadrant pain, clonus

tocols have been developed for intensive home monitoring of women with mild preeclampsia after initial hospitalization. The burden of proof of their safety in comparison to hospitalization rests with their advocates.

There is no reason to delay delivery if the pregnancy has reached 36 weeks gestation. Other indications for delivery include any manifestation of the HELLP syndrome, neurologic symptoms, rising serum creatinine, a blood pressure > 160/110 after 24 hours of hospitalization, and impending or actual seizures. Attempts have been made to manage severe preeclampsia at < 28 weeks gestation [35] and even to prolong pregnancy following a seizure, but we consider this approach too dangerous for general use.

Seizure prophylaxis is required while preparations for delivery are made. There has been a long-standing transatlantic difference in the approach to seizure prevention. Magnesium sulfate has been widely used in the United States, while European centers have favored other anticonvulsants, such as phenytoin and benzodiazepines. Magnesium sulfate appears to be preferable, based on a large, prospective, randomized study [18] in 1089 preeclamptic women assigned to treatment with phenytoin and 1049 assigned to treatment with magnesium sulfate. There were 10 instances of eclampsia in the phenytoin-treated group, but none in the magnesium-treated women. Magnesium sulfate was also more effective than phenytoin and diazepam for prevention of recurrent seizures in 1687 women who had had eclampsia [36]. The mechansim of action of magnesium sulfate has been attributed to its direct vasodilator effect and a possible effect in increasing prostacyclin production. It should be remembered, however, that magnesium sulfate is excreted by the kidneys, and oliguric women or women with preexisting renal insufficiency should be monitored carefully and treated with lower doses. Magnesium is a calcium channel blocker and its use with other calcium channel blockers may result in profound hypotension.

The combination of sodium retention and intravascular volume contraction have led to treatment of preeclampsia with both diuretics and with volume expansion. Both approaches are misguided. Diuretics aggravate hypoperfusion of vital organs and should be reserved for women with congestive heart failure. Volume expansion increases the risk of pulmonary edema. Hemodynamic monitoring by Swan-Ganz catheter is advised before using either of these interventions.

Treatment of hypertension does not reverse preeclampsia, and may even disguise progression, but is required to prevent the most severe complications of preeclampsia, including cerebral hemorrhage. Treatment is usually started when the diastolic blood pressure is 105 mm Hg but should be instituted earlier in women with very low blood pressures early in pregnancy. The drugs used to treat hypertensive emergencies in pregnancies are discussed below. The goal of blood pressure reduction is a diastolic blood pressure of 90 – 100 mm Hg.

Chronic Hypertension

Essential hypertension more often affects mothers in the later childbearing years. With the growing number of late pregnancies and even postmenopausal pregnancies, the importance of this problem can be expected to increase.

Almost half of the women with essential hypertension have a fall in blood pressure into

the normal range during the second trimester with a return to baseline elevated levels in the third trimester. This drop makes it difficult to determine whether a woman seen for the first time in the second trimester with normal blood pressure has essential hypertension or preeclampsia when the blood pressure rises in the third trimester.

Women with chronic hypertension have an increased risk of preeclampsia, perinatal mortality, small for gestational age (SGA) babies, premature delivery, and, in some series, gestational diabetes [37].

Women with severe essential hypertension (BP > 170/110) are at the greatest risk for preeclampsia and are also at risk for cerebral hemorrhage and abruptio placentae. The frequency of superimposed preeclampsia in this group is high: 52% in one group of 44 such women [38]. The perinatal mortality was 25% in the latter report. Seventy percent of infants were premature and 43% were SGA. Maternal complications included one instance of abruptio placentae, deterioration of renal function in 20 (permanent), and one episode of hypertensive encephalopathy. The frequency of superimposed preeclampsia in women with mild hypertension ranges from approximately 5.2 – 18.4%. Maternal and fetal morbidity are increased even with mild hypertension, but the efficacy of pharmacologic treatment in preventing complications in women with mild hypertension and the level of blood pressure at which treatment should be instituted are a matter of debate. There is conflicting evidence whether treatment of mild hypertension prevents worsening of hypertension later in pregnancy and whether treatment lowers perinatal mortality [39 – 43]. We take the position that safe medications are available for the treatment of hypertension during pregnancy, and treatment should begin at a blood pressure > 140/90.

Antihypertensive Medications

The effects of various antihypertensive medications in pregnancy are reviewed in Table 5. The Food and Drug Administration (FDA) designation (see appendix for explanation) is included, but does not adequately reflect the risks and safety of the various drugs.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors are contraindicated in pregnancy. Animal studies reported a high frequency of stillbirths in animals exposed to ACE inhibitors during pregnancy, resulting in a recommendation against their use in human pregnancy by a committee of the National Institutes of Health [44]. Exposure to ACE inhibitors in the second and third trimester has been associated with renal tubular dysplasia, hypocalvaria, hypoplastic lungs and limb contractures [45]. Renal tubular dysplasia has been attributed to fetal hypotension and decreased renal perfusion. ACE inhibitors are associated with decreased fetal urine output and oligohydramnios. Amniotic fluid is required for normal pulmonary development, and oligohydramnios is responsible for the instances of hypoplastic lungs. Many of the neonatal deaths in infants exposed to ACE inhibitors are the result of respiratory failure. Oligohydramnios also accounts for limb contractures. Direct pressure of the uterine muscle on the fetal skull is thought to result in abnormal calcification of the skull. Several instances of patent ductus arteriosus have been described. This effect is thought to be the result of the effects of ACE inhibitors on prostaglandin metabolism.

Two studies, involving 46 and 86 infants, respectively, showed no adverse effect of exposure to ACE inhibitors in the first trimester

Table 5. Antihypertensive Drugs in Pregnancy

Drug (Category)	Comments
Chronic hypertension	
ACE inhibitors(D)	Contraindicated. 2nd and 3rd trimester use associated with pulmonary hypoplasia, hypocalvaria, renal dysplasia, neonatal anuria, contractures. No known harm in 1st trimester.
Methyldopa (C)	Safe. 40-year use. Careful developmental testing of children at ages 4 and 7.
Beta Blockers (C)	Probably safe. Fetal bradycardia, hypoglycmia, respiratory depression at birth, intrauterine growth restriction
Labetolol (C)	Limited first trimester experience. Less bradycardia and growth restriction than β blockers.
Clonidine (C)	Probably safe. Limited 1st trimester exposure.
Calcium channel blockers (C)	Profound hypotension with when used magnesium. Limited experience. Reserve for severe hypertension.
Hydralazine (C)	Safe. Long experience with use in pregnancy. No increase in birth defects.
Minoxidil (C)	Very limited experience. Hypertrichosis in the infant.
Prazocin (C)	Limited experience. No problems noted.
Thiazide diuretics (D)	Increased congenital anomalies with chlorthaldone. Decreased intravascular volume expansion,neonatal thrombocytopenia, hemolytic anemia, electrolyte abnormalities
Hypertensive crisis	
Hydralazine (C)	Used for 40 years without serious side effects
Labetolol (C)	Shorter length of use. Appears safe.
Nitroprusside (C)	Fetal cyanide toxicity
Diazoxide (C)	Fatal maternal hypotension reported. Limit dose to 30 mg boluses. Decreased uterine contraction. Neonatal hyperglycemia.

[46]. In the latter report, there were 4 congenital anomalies, a number not significantly different from the 3 expected [46]. However, our understanding of the role of the renin-angiotensin system in early renal development is incomplete, and an as-yet unrecognized adverse effect of ACE inhibitors on this process is possible. The absence of demonstrated ill effects of ACE inhibitors following first trimester exposure is of considerable importance. Women with inadvertent first trimester exposure need not be advised to terminate the pregnancy. A more important issue is whether women with nephropathy taking ACE inhibitors for their renoprotective effect need to discontinue them in planning for pregnancy if there is some assurance that pregnancy can be diagnosed promptly and the drug stopped at that point. For women with normal renal function where conception can be expected to occur within a year, stopping ACE inhibitors in planning pregnancy is warranted. However, for women with moderately impaired renal function who may not conceive for years, discontinuation of ACE inhibitors may not be necessary.

There is less experience with Ang II receptor blockers, but it is expected that problems caused by decreased angiotensin effect will be similar.

Diuretics

The obstetric community is strongly averse to using diuretics during pregnancy. At one point, diuretics were widely used in the hope that by reducing edema and hypertension might prevent preeclampsia. These drugs did not prove to be effective for this purpose, and they aggravated the decreased intravascular perfusion seen with preeclampsia, possibly contributing to organ hypoperfusion [47]. The failure of diuretics to prevent preeclampsia now discounts the observation that their use in women with edema was rarely associated with adverse effects. A report documenting a subnormal expansion of intravascular volume in women with essential hypertension treated with diuretics did not show increased perinatal mortality [48]. For essential hypertension, other drugs are preferred, but diuretics may be useful in hypertension associated with renal insufficiency and salt-sensitive hypertension. There are some reports of neonatal thrombocytopenia, hemolytic anemia, jaundice, and electrolyte abnormalities with thiazides, but most of the concern about their use centers on their effects on intravascular volume [49, 50].

Beta Blockers

There have been several case reports of neonatal bradycardia, hypoglycemia and respiratory depression associated with beta blockers, but these problems are generally easily managed by the neonatologist [51]. Data are mixed concerning whether beta blockers are associated with IUGR and there are reports of SGA infants born to mothers treated with beta blockers for diseases not usually associated with growth restriction [52]. There are also data from animal models suggesting a decreased ability of the fetus to withstand anoxic stress [53]. None of these problems has turned out to be a major contraindication to the use of this category of drugs. Fetal bradycardia may make it difficult to interpret antenatal monitoring, which depends on changes in fetal heart rate.

Labetolol

Labetolol is not associated with fetal bradycardia and IUGR and it is widely used in preference to beta blockers. Nonetheless, data on first trimester effects of the drug are still limited. Moreover, controlled studies have not shown it to be superior to other antihypertensive agents [41, 46, 54].

Methyldopa

Methyldopa has been used in pregnant women for over 40 years and is still the drug of choice for essential hypertension. Careful developmental studies have been done in children at 4 and 7 years of age exposed to the drug in utero, and no problems have been found [55]. One study of 242 women with diastolic blood pressures of 90 – 110 mm Hg randomized to treatment with methyldopa versus placebo showed decreased fetal loss in the methyldopa-treated group [56].

Clonidine

Clonidine is a centrally acting α2-agonist reported in one study to have efficacy and safety similar to methyldopa [57]. In view of the limited experience with it, there is no reason to use it in preference to methyldopa.

Calcium Channel Blockers

Nifedipine, nicardipine, and verapamil have been used in severe hypertension. They do not appear to be associated with any increase in congenital anomalies when used in the first trimester. These drugs have been used for tocolysis in the third trimester. There is limited experience with diltiazem. Calcium channel blockers may potentiate the hypotensive effects and neuromuscular blockade of magnesium, and the interaction should be kept in mind when the drugs are used in women at risk for preeclampsia [58, 59]. Because of limited experience, their use is best restricted to severe hypertension unresponsive to other drugs.

Prazocin

No adverse effects on the fetus have been demonstrated with prazocin drugs, but the experience with it is more limited than with labetolol, methyldopa, and β blockers, and it does not appear to offer any advantage. The drug can be continued in women whose blood pressure is well controlled on it at the time of conception.

Hydralazine

Hydralazine has been used safely during pregnancy for 40 years. It is ineffective as a single oral agent but can be added to a first-line drug if the latter is ineffective alone.

Minoxidil

The more potent vasodilator, minoxidil has been associated with hypertrichosis and congenital anomalies in one case report [60]. It is ineffective unless combined with a diuretic and a sympatholytic agent.

Drugs for Hypertensive Emergencies

Hydralazine

Intravenous hydralazine in doses of 5–10 mg every 20 – 30 minutes is the drug of first choice for hypertensive crisis in pregnancy. A single study has shown a higher frequency of malignant ventricular arrhythmias in eclamptic women treated with hydralazine than in women treated with labetolol [61]. Nine studies comparing hydralazine with other drugs, most often intravenous labetolol, have found no advantage of one drug regimen over another [62].

Labetolol

Intravenous labetolol given either as a 20 mg loading dose followed by 20 – 60 mg every 30 minutes, or a 1 – 2 mg/min drip is the second most commonly used regimen for treating hypertensive emergencies in pregnant women. There are occasional reports of fetal bradycardia, and the newborn should be monitored for hypotension.

Diazoxide

There is extensive experience with the use of diazoxide in pregnancy, but the drug is now primarily of historic interest. In doses of 150 – 300 mg, it has been associated with at least one maternal fatality from hypotension. It is also associated with decreased uterine contractions and neonatal hyperglycemia. Its only

advantage is a long duration of action, which may make it useful in a woman who must be transported with minimal monitoring capability, or when other drugs have failed. It should be used only in 30 mg boluses every 1 – 2 minutes until the desired blood pressure is reached.

Nitroprusside

Nitroprusside carries the risk of fetal cyanide toxicity, and it should be used with caution, especially in women with renal insufficiency.

Nifedipine

Because of its interaction with magnesium sulfate and the general movement away from using short-acting nifedipine for hypertensive emergencies in nonpregnant patients, nifedipine should not be used as a first-line drug in hypertensive emergencies of pregnancies.

Chronic Hypertension with Superimposed Preeclampsia

Ten percent of women with mild hypertension and up to 50% of women with severe hypertension develop superimposed preeclampsia. The diagnosis depends on an increase in blood pressure over baseline levels and development of proteinuria. Since there is frequently a modest increase in blood pressure in hypertensive women in the third trimester, proteinuria is more important to the diagnosis. The absolute level of blood pressure is frequently higher in these women than in women with isolated preeclampsia. It is the group of women with superimposed preeclampsia in whom the frequency of abruptio placentae and cerebral hemorrhage is increased.

Secondary Hypertension in Pregnancy

Secondary hypertension in pregnancy is generally uncommon, but several causes bear discussion.

Pheochromocytoma

Pheochromocytoma is exceedingly rare, but is associated with a 50% maternal mortality rate if it is undiagnosed, and it should be excluded if the suspicion arises [63]. The maternal mortality rate is 11%, even if the diagnosis is made antepartum. Catecholamines do not cross the placenta and the fetus is not exposed to high levels, but there may be placental hypoperfusion secondary to vasoconstriction. Hypertension can be precipitated by labor. Urine and plasma norepinephrine and epinephrine are unchanged in normal and preeclamptic pregnancy, and the usual biochemical screening can be used. Surgery is generally the treatment of choice after two weeks of treatment with α blockers. An unusual complication of pregnancy is compression of an extra-adrenal pheochromocytoma located at the aortic bifurcation in the organ of Zuckerkandl by the expanding uterus.

Cocaine

Cocaine use is a common cause of secondary hypertension in young women and may

have a similar clinical presentation to pheochromocytoma. Serum and urine screening usually makes the diagnosis and α blockers are required for treatment. Cocaine use is associated with an increased risk of abruptio placentae [64].

Hyperaldosteronism

Hyperaldosteronism is uncommon in pregnancy. Basal aldosterone levels in pregnancy are elevated but are suppressible by salt loading and exogenous mineralocorticoid [63]. Plasma renin is usually but not always, suppressed rather than showing the usual pregnancy-associated elevation. Progesterone counteracts the potassium-wasting effect of aldosterone, and hypokalemia may be absent. Bilateral disease is treated medically. Spironolactone, used in nonpregnant individuals, is an antiandrogen and may cause abnormal genital development in male fetuses. Amiloride can be used in pregnancy to treat primary hyperaldosteronism.

Renal Artery Stenosis

Renal artery stenosis is uncommon, and its effect on pregnancy is related to the severity of the hypertension. Management is complicated by the inability to use ACE inhibitors, but other medications are frequently effective. Angioplasty has been successfully carried out during pregnancy [65].

Long-Term Prognosis of Hypertensive Disorders

Studies of the long-term effects of hypertensive disorders of pregnancy have been confounded by the failure of many reports to distinguish preeclampsia from chronic hypertension. Chesley followed 270 women who had survived eclampsia in a landmark study of the long-term consequences of the disease. Only one-third of the women who had subsequent pregnancies developed hypertension. In a separate study of 354 subsequent pregnancies in 151 nulliparous women who survived eclampsia, severe preeclampsia recurred in 5.3% and eclampsia recurred in 2% [66]. The risk of recurrence of the HELLP syndrome is approximately 20% [67]. Chesley followed 197/206 nulliparous women with eclampsia for an average of 33 range (23 – 42) years, by which time > 81% of the women were older than 50 years of age [68]. The frequency of hypertension, mortality (16.6%) and cardiovascular mortality (4.8%) in white women was similar to the general population. Mortality in 19 nulliparous black women who survived eclampsia was twice that of white women, but was not increased compared to the general black population. The mortality rate for the 59 multiparous white women was 56%, but 100% and for the 5 black multiparous women surviving eclampsia. By using eclampsia to define the group, Chesley excluded women with simple chronic hypertension, while including women with preeclampsia superimposed on chronic hypertension. The conclusion is that preeclampsia is a predictor of mortality and cardiovascular disease only when it is superimposed on essential hypertension.

Renal Infections in Pregnancy

Asymptomatic bacteriuria, defined as > 10^5 colony-forming units (CFU) of a single organism cultured from a clean-catch midstream urine specimen, occurs in 5% to 10% of pregnancies. While this frequency is no higher than for normal nonpregnant women, the consequences are greater, as up to 30% of pregnant women with asymptomatic bacteriuria will go on to develop pyelonephritis if untreated [69]. In recent years, screening programs and treatment of asymptomatic bacteriuria have led to a decline in the frequency of pyelonephritis in pregnant women. In one report, the incidence of pyelonephritis declined from 1.8% – 0.6% of pregnancies [70]. Screening by urine culture should be done at the first prenatal visit. Other tests for bacteriuria, such as urine dipstick for nitrate and leukocyte esterase, have not proven to be sensitive enough for use in screening [71], and the urine sediment may contain an increased number of white blood cells during pregnancy, even in the absence of infection.

A positive urine culture should be treated for 7 – 10 days with antibiotics chosen on the basis of sensitivity of the organism and safety in pregnancy. Surveillance cultures should be done a week after the completion of treatment and every 4 – 6 weeks thereafter to monitor for relapse. A second positive culture warrants another course of treatment, and a relapse within a week of the initial antibiotic therapy should be treated with a different drug. For patients who relapse a second time, the usual course of antibiotics is followed by suppressive therapy for the rest of the pregnancy. Women with 2 or more relapses should undergo urologic evaluation when they are 12 weeks postpartum, i.e. after pregnancy-induced changes in the urinary tract have had sufficient time to revert to normal [69, 72]. Patients who have a negative urine culture at initial evaluation and no other risk factors for urinary tract infection do not need additional testing unless symptomatic. In most cases, asymptomatic bacteriuria represents a preexisting condition, because the risk of acquiring asymptomatic bacteriuria during pregnancy peaks near term at 2% [73].

The most commonly occurring organisms in asymptomatic bacteriuria are gram negative bacteria, with *Escherichia coli* responsible for up to 90% of positive cultures, followed by the *Klebsiella Enterobacter* group (5 – 15%), *Proteus* species (1 – 10%), and gram positives such as coagulase-negative *Staphylococcus* (1 – 11%), *Streptococcus faecalis* (1 – 4%), and group B *Streptococcus* (1 – 4%). Antibiotics should be chosen carefully in pregnancy. Ampicillin is safe in pregnancy; however, up to 30% of E. coli are resistant to it [69], and antibiotic sensitivities are continuously changing. First-generation cephalosporins, e.g. cefazolin and cefalexin, are safe in pregnancy. Cephalosporins with a methyltetrathiazole moiety (cefoperozone, cefotetan, moxalactam, and cefamandole) are usually avoided in pregnancy because studies have shown infertility in animals [74]. Nitrofurantoin, an antibiotic specific for the urinary tract, is safe in pregnancy and effective against the most common causative organisms. It cannot be used in women with renal insufficiency. It can cause hemolysis in the male fetus of a woman who carries glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, and patients should be screened for this history prior to use. Sulfa drugs, such as sulfamethoxazole, can be used in the early part of pregnancy but should be avoided in the latter part because of the risk of kernicterus. Trimethoprim and trimethoprim-sulfamethoxizole combinations are generally avoided because of the

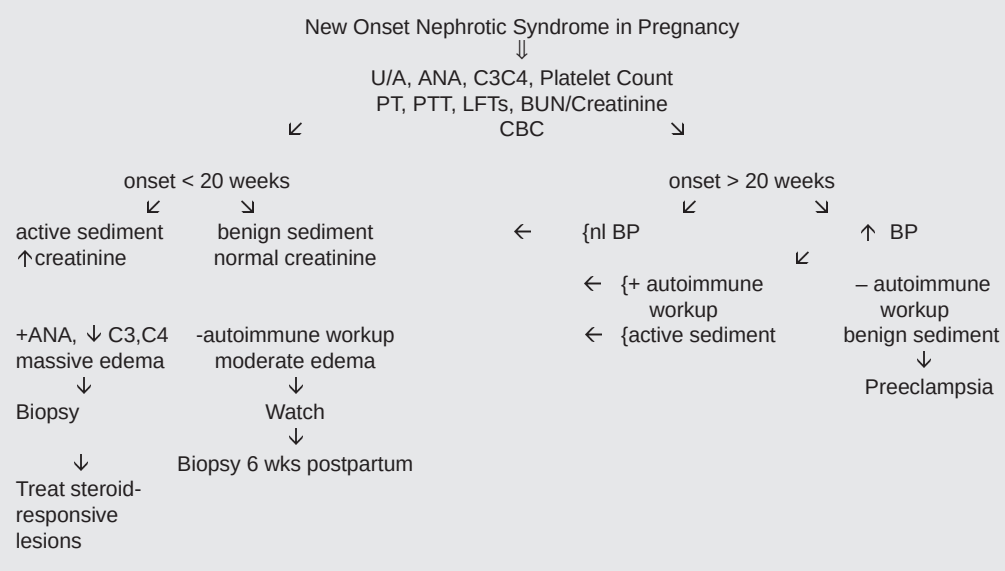

Figure 1. New Onset Nephrotic Syndrome in Pregnancy.

teterogenicity of folic acid antagonists. In practice, significant increases in congenital anomalies have not been noted with these drugs. The quinolone antibiotics should be avoided in pregnancy because they have been associated with weakened cartilage in young animals. Aminoglycosides should also be avoided because of their association with eight nerve damage [74].

Pyelonephritis in pregnancy is a severe infection associated with bacteremia, hypotension, premature labor, and, in 2% of patients with respiratory failure. Pyelonephritis during pregnancy is often associated with a decline in GFR. In a study of 220 women hospitalized for pyelonephritis, Whalley and colleagues observed that 25% of women had a creatinine clearance < 80 cc/min [75]. On reevaluation 3 – 8 weeks after treatment, 18 women whose creatinine clearance had fallen to < 70 mL/min had had a return to normal or near-normal renal function. Pregnant women with pyelonephritis should be treated aggressively with antibiotics and fluid resuscitation. Hospitalization and initiation of intravenous antibiotics have been the traditional standard of care. Relatively stable pregnant patients with pyelonephritis treated on an outpatient basis with intramuscular ceftriaxone showed recurrence rates similar to those of women treated with intravenous cefazolin. Antibiotic therapy should be continued for 2 weeks, and suppressive therapy may be continued for the remainder of the pregnancy. Women who fail to improve within 3 days of antibiotic therapy should undergo ultrasound evaluation to rule out nephrolithiasis. Ultrasound may be difficult to interpret because of hydronephrosis and, if suspicion is high, additional radiographic tests may be needed.

Nephrolithiasis in Pregnancy

Several changes in pregnancy might be expected to lead to increased stone formation. Urinary stasis in the dilated collecting system is accompanied by hypercalciuria, increased supersaturation levels of calcium, oxalate, and phosphate, and an alkaline urine. However, there is an increased excretion of magnesium citrate as well as the glycoprotein nephrocalcin, which inhibit stone formation [76]. Nephrolithiasis is a common cause of abdominal pain in pregnant women and may be overlooked when evaluation focuses solely on obstetric problems. The seriousness of infection associated with stone disease outweighs any potential adverse fetal effect of radiation required to diagnose and treat stone disease. Stones may be difficult to visualize on plain abdominal films because they may be obscured by the fetal skeleton late in pregnancy, and ultrasound is difficult to interpret. Intravenous pyelography (IVP) or spiral CT scan can be used to diagnose and locate the stone. Retrograde pyelography for diagnostic purposes or stent placement can be performed but requires considerable urologic finesse late in pregnancy. The effects of lithotripsy during pregnancy are not known, and it should not be used.

Development of Proteinuria

When proteinuria develops de novo in a woman receiving regular prenatal care, much of the diagnostic evaluation has already been done: glucose tolerance testing, screening for infectious causes of nephrotic syndrome, e. g. HIV, hepatitis B and C, and syphilis, and a history of prescription, over-the-counter and illicit drug use. The remaining crucial issues that need to be addressed are presented in Figure 1.

Diagnosis of Preeclampsia

Preeclampsia is the most common cause of proteinuria in pregnant women, and most women are presumed to have preeclampsia unless there is some atypical feature that points to another renal disease. The likelihood of another renal disease is very high if the onset of proteinuria occurs before 20 weeks gestation, if there is no hypertension, if there is an active urine sediment, or if serum complements are depressed. Only 25% of multigravidas with proteinuria have uncomplicated preeclampsia [77], but previous pregnancy is not as strong an indicator of other renal disease as are the other factors mentioned previously.

When to Biopsy for Proteinuria

Diagnosis of Systemic Lupus Erythematosis (SLE)

SLE is the other most important cause of proteinuria which presents more frequently during pregnancy. Usually SLE can be distinguished from preeclampsia by an active urine sediment or positive lupus serologies. Both SLE and preeclampsia can be multisystem diseases, and there is some overlap in their extrarenal manifestations. Thrombocytopenia and hemolytic anemia are common manifestations of both. In preeclampsia, hemolytic anemia is distinguished by microangiopathic changes on peripheral smear. Both SLE and preeclampsia may be characterized by hyper-

tension, rapidly progressive renal failure, and seizures. The pulmonary hemorrhage of SLE may appear similar on chest X-ray to pulmonary edema in preeclampsia. However, pericarditis, joint pain, and skin rash are not characteristic of preeclampsia, and markedly elevated transaminases are not common in SLE. If thrombocytopenia occurs before hypertension and proteinuria, the possibility of SLE arises. When the diagnosis of SLE is made or strongly suspected during pregnancy, a renal biopsy is warranted. SLE that develops during pregnancy frequently has the histology of diffuse proliferative glomerulonephritis and may require the prompt initiation of aggressive treatment.

Loss of Renal Function (See Acute Renal Failure)

When there is a deterioration of renal function during pregnancy and the cause is not apparent, biopsy should be done. Usually the diagnosis of preeclampsia or hemolytic uremic syndrome (HUS) as a cause of proteinuria and rising serum creatinine can be made without biopsy. Acute glomerulonephritis may require biopsy to determine whether treatment is indicated or likely to be effective.

Severe Nephrotic Syndrome

When renal function and blood pressure are normal in a patient who appears to have a primary renal disease, it is not usually necessary to make a specific histologic diagnosis. Occasionally the edema and hypoalbuminemia associated with nephrotic syndrome are so severe that treatment with steroids is considered. In this situation, renal biopsy is helpful. High-dose steroids have been used extensively in pregnancy for a wide variety of conditions, but are associated with an increased risk of hypertension and glucose intolerance as well as adrenal suppression in the infant. Their use should be confined to minimal change disease (MCD) or focal sclerosis where there is a substantial chance of response. In patients with focal sclerosis, treatment should be continued only in women who have an early response (within a month) rather than using a prolonged trial that might be undertaken in a nonpregnant patient.

Differentiating Preeclampsia from Primary Renal Disease

In some situations, it is difficult to distinguish between primary renal disease and preeclampsia. Since the definitive treatment for preeclampsia is delivery, certainty about the diagnosis has therapeutic implications. Practically, it is rarely possible to take advantage of a brief window of opportunity when proteinuria is heavy enough to raise the question of another renal disease and before the blood pressure is too high to do the biopsy safely.

In some women, pregnancy is the first occasion for a urinalysis in adult life, and the discovery of proteinuria at the first prenatal visit may reflect preexisting renal disease. The distinction between preeclampsia and primary renal disease is made on the basis of the same diagnostic features that differentiate the two diseases when the onset of proteinuria is known to have occurred during pregnancy.

Treatment of Nephrotic Syndrome

Treatment of nephrotic syndrome unresponsive to steroids is problematic during pregnancy. Proteinuria increases during pregnancy and edema may become massive, lead-

ing, in some cases, to skin breakdown and bladder outlet obstruction. Low doses of diuretics have been shown to be fairly low risk in the absence of preeclampsia, and the use of low-dose diuretics in women with disabling edema is reasonable. Unfortunately, patients with nephrotic syndrome frequently require doses much higher than those shown to be safe in studies of pregnant women. When furosemide is used in pregnant women, fetal urine output increases, and high doses might be expected to carry the risk of volume contraction and electrolyte abnormalities in the fetus. Pregnancy may aggravate the hypercoagulability associated with nephrotic syndrome. Women with previously documented renal vein thrombosis should be fully anticoagulated with heparin throughout pregnancy. Although there are no clear data, it is reasonable to give low-dose heparin (5000 U subcutaneously twice daily) to women with membranous nephropathy and profound hypoalbuminemia (albumin < 2 g/dL). Treatment of elevated cholesterol should be deferred until after delivery because lovostatin has been associated with congenital anomalies.

Chronic Renal Disease

Hypertension

Hypertension is a common complication of pregnancy in women with renal disease even with good renal function. Worsening hypertension is usual. The diagnosis of preeclampsia can be difficult because all manifestations of preeclampsia can occur from the renal disease itself. The approach to the control of blood pressure in women with preexisting renal disease is similar to that in women with chronic hypertension, but control of blood pressure should be initiated early and an attempt should be made to keep the blood pressure < 140/90. We recommend teaching women with underlying renal disease to measure their own blood pressure at home between obstetric visits because increases in blood pressure can be abrupt.

Proteinuria

Proteinuria generally increases in women with glomerular disease and preexisting proteinuria who become pregnant, but pregnancy does not precipitate a relapse in women whose nephrotic syndrome is in remission [78]. Heavy proteinuria early in pregnancy has been associated with an increased rate of fetal loss, prematurity, and IUGR, an observation that provides support for steroid treatment of susceptible lesions. Nephrotic-range proteinuria occurring later in pregnancy does not adversely affect fetal outcome.

Accelerated Decline in Renal Function

The most important determinant of the effect of pregnancy on underlying renal disease is the level of renal function at the time of conception rather than the nature of the underlying renal disease. If a woman with renal disease conceives when her renal function is normal or only mildly decreased, the progression of her renal disease is not usually accelerated, although her pregnancy is still likely to be complicated by hypertension and increased proteinuria [79]. Three retrospective studies examined the course of renal disease in women who had a least one pregnancy compared with concurrent controls [80 – 82]. The largest study included 171 women with a

variety of glomerular diseases who became pregnant and 189 women who did not become pregnant after the onset of glomerulonephritis. There was no difference in the frequency of ESRD with a mean follow-up of 15 years [81].

In contrast, decline in renal function accelerated in women with moderate to severe renal insufficiency who become pregnant. There is disagreement about the level of renal function at which pregnancy becomes a factor in the acceleration of the disease, but the most widely used marker is a serum creatinine of 1.4 mg/dL. Multiple studies support this observation [83 – 86], but are flawed because of small numbers and the absence of controls. A larger report published in 1996 included 82 pregnancies in 67 women with primary renal disease and serum creatinine of 1.4 mg/dL. prior to conception or in the first trimester [87]. Twenty percent of women had a deterioration in renal function during pregnancy, and 23% had a deterioration in the first 6 weeks postpartum. At 6 months postpartum, 8% had recovered renal function and an additional 10% had deteriorated. The likelihood of an accelerated decline in renal function was greater in women whose first measured serum creatinine was > 2 mg/dL. One of 49 women with serum creatinine between 1.4 and 1.9 mg/dL. experienced accelerated decline, in contrast to 7/ 21 pregnancies in women with serum creatinine of ≥ 2.0 mg/dL. Eight women progressed to ESRD within a year of pregnancy, including 7 women with pregnancy-associated decline in renal function.

With the obstetric and neonatal care currently available, fetal survival in the setting of chronic renal disease is high. The fetal prognosis even for women who conceive with impaired renal function has improved over the last 2 decades. Several recent outcome studies have reported fetal survival > 90% in such pregnancies [87, 88] and infant survival > 70% even in pregnancies in women whose renal function deteriorated to the point of needing dialysis [89]. Prematurity and IUGR, however, are still common. Over 70% of infants are born prematurely in some series [84, 85, 87], and the frequency of IUGR from 43 – 57% [84, 87].

Arguments have been made that the outcome of pregnancy and the effect on maternal disease is worse in certain glomerular diseases, including IgA nephropathy, focal segmental glomerulosclerosis (FSS), and membranoproliferative glomerulonephritis (MPGN) [78]. However, there is no solid evidence that the risk factors for poor outcome in these diseases, specifically hypertension and renal insufficiency, are different from other renal diseases.

Diabetic Nephropathy

At least 4 reports involving 136 women with diabetes mellitus (DM) and nephropathy conclude that pregnancy does not have an adverse effect on the progression of the disease [90 – 93]. Most of the reports investigating the effect of pregnancy on established diabetic renal disease included very few women with impaired renal function. Only 12 of the 90 women in the reports that gave individual baseline renal function had initial serum creatinine > 1.4 mg/dL. At least 6 of these women experienced an accelerated progression of renal disease during pregnancy. In one study in which 12 women had ESRD at follow-up, it was unclear whether these were women with preconception serum creatinine ≥ 1.4 mg/dL. Purdy and colleagues recently reported on 14 pregnancies in 11 women with

diabetic nephropathy and serum creatinine of ≥ 1.4 mg/dL prior to pregnancy or in the first trimester. Forty-five percent of the women showed accelerated progression of renal disease [94], as determined by a change in the slope of 1/Cr during pregnancy and postpartum, and by comparison with a nonpregnant control group. Another report of 7 pregnancies in 6 patients with preconception serum creatinine of 1.5 mg/dL found no change in the slope of 1/Cr, but 3 women had reached ESRD at 30-month follow-up [95]. In diabetic nephropathy, as in other renal diseases, the level of renal function at conception is the most important determinant of the effect of pregnancy on the progression of the disease.

Patients with diabetic nephropathy, with or without severe renal insufficiency, have a high frequency of hypertension during pregnancy (53 – 97%). Hypertension is common before pregnancy, frequently worsens during gestation, and often develops in previously normotensive women. DM is a recognized risk factor for preeclampsia, but even low level proteinuria (190 – 499 mg/24 hours) identifies a group at higher risk for preeclampsia than women with diabetes alone [96]. Coombs and colleagues followed pregnancies in 311 women with DM with varying degrees of first trimester proteinuria. For women with 24 hours urine protein < 190 mg/day, the risk of preeclampsia was 10%, only slightly higher than the general population. The risk of preeclampsia in the groups with 190 – 499 mg/day and ≥ 500 mg/ day was 40% and 47%, respectively.

Proteinuria increases during pregnancy in women with diabetic nephropathy, as it does in women with other renal diseases. The frequency of nephrotic-range proteinuria in the 5 reports cited above ranged from 41 – 73%. Nephrotic-range proteinuria develops in > 50% of women who have lower levels of proteinuria before conception.

Despite serious maternal problems, long-term infant survival was > 95% with no stillbirth or neonatal death in the two reports of women with moderate renal insufficiency. However, approximately half of the infants were born prematurely and 15% had long-term developmental problems, often related to congenital anomalies resulting from poor glucose control during organogenesis.

Lupus Nephritis

Course of Lupus Nephritis in Pregnancy

Although some investigators argue that pregnancy per se does not aggravate lupus nephritis, the bulk of the data supports the contention that pregnancy has an adverse effect on the course of the disease, and there is a risk of renal failure and even death in women with lupus nephritis who become pregnant. In 276 women reported in 19 studies who had a diagnosis of lupus nephritis at conception, 133 (48%) experienced a worsening of renal disease during pregnancy [97 – 115]. Thirty exacerbations were characterized by ARF and, of these, 18 progressed to ESRD or resulted in maternal death. An additional 8 had a decline in renal function that was permanent but did not lead rapidly to ESRD. At least 44 women became nephrotic. Even in the absence of evidence of a lupus flare, hypertension and preeclampsia were common, and episodes of eclampsia were reported. While the majority of studies were uncontrolled, several studies using both nonpregnant women and the index subjects before and after

pregnancy as controls showed an increase in the frequency of SLE flares during pregnancy. In studies where renal histology was known, the frequency of exacerbations during pregnancy was higher for women with membranous nephropathy than for those with diffuse proliferative glomerulonephritis, even though membranous lupus is generally thought to have a more indolent course. Women with lupus nephritis were also at risk for severe extrarenal manifestations of SLE, including cerebritis, pericarditis, and mesenteric vasculitis. The risk of exacerbation is lower in women whose disease has been in remission for > 6 months before conception [101].

Effects of SLE on the Fetus

Several characteristic problems occur in the infants of women with SLE. Women with anticardiolipin antibody have an increased risk of fetal loss [116]. Several studies of prednisone treatment for this disorder show no benefit from steroid treatment. Many lupus-associated autoantibodies are IgG and cross the placenta. Neonatal lupus may be associated with skin rashes, thrombocytopenia, and hemolytic anemia [117]. These manifestations resolve over 6 months as maternal antibody disappears. Anti-SSA is deposited in the conducting system of the fetal heart and is associated with irreversible congenital heart block [118 – 120]. Some infants die in childhood from related myocardial fibrosis and heart failure, and others require long-term pacemakers.

Pregnancy in Renal Transplant Recipients

Over 6,000 pregnancies have been reported in women of childbearing age who have received a renal transplant. Transplant recipients are advised to wait 2 years after transplantation before contemplating pregnancy. Pregnancy should be undertaken only if blood pressure is controlled and renal function is stable with a serum creatinine of < 2.0 mg/dL.

Effect of Pregnancy on Graft Function

The question has been raised whether the hyperfiltration that occurs during pregnancy might have a detrimental effect in women with renal transplants whose GFR is lower at conception than in healthy women. Permanent loss of graft function during or after pregnancy in women with renal transplants is approximately 10% in a large number of reports. Several case-control studies have attempted to determine whether decline in renal function was caused by pregnancy [121 – 124].

First and colleagues reported on graft function in 18 women who underwent 25 pregnancies, compared with 26 female controls and 23 male controls [121]. Mean follow-up for the women who became pregnant was 11.8 years after transplantation and 6.9 years after pregnancy, with similar periods of follow-up for the control groups. At last follow-up, graft survival was 77.8% in women who had become pregnant, 69.2% in the female controls, and 69.8% in the male controls (NS). Both women who had become pregnant and the female controls had had an increase in serum creatinine over time. However, only 3 women

had serum creatinine > 1.5 mg/dL at conception, and in only one was it > 2.0 mg/dL. Only 5 of the 18 women who became pregnant were treated with cyclosporine.

A single controlled study suggests that graft function is adversely affected by pregnancy [122]. Salmela et al. reported on long-term graft function in 22 female transplant recipients with 29 pregnancies, compared to 38 female controls matched for cause of renal failure, kidney source, immunosuppression, time from transplantation, and serum creatinine. During the follow-up period, 8 of the women who became pregnant lost their grafts, one at one month postpartum. The remainder of the grafts were lost between one and 11 years postpartum, but deterioration of graft function began during pregnancy in 3 women. At 10-year follow-up, graft survival was 100% for the control group and 69% for the group who had had pregnancies ($p < .005$). Graft loss could not be correlated with elevated serum creatinine at the time of conception. The general applicability of the conclusions drawn in this report is limited by the paucity of centers achieving 100% 10-year graft survival similar to what was seen in the control group.

Infection

UTIs are the most common bacterial infections in pregnant transplant recipients, occurring in 40% of pregnancies [125]. Monthly urine cultures and prompt treatment of asymptomatic bacteriuria are needed. The pathogenic organisms occurring in immunosuppressed patients that are of particular concern for pregnant women are Listeria, Herpes, Cytomegalovirus (CMV) and Toxoplasma. Transplant recipients should be evaluated for previous infection with the latter 3 before pregnancy or at the first prenatal visit.

Immunosuppressive Drugs in Pregnancy

Cyclosporine

There are a number of theoretical concerns about cyclosporine metabolism in pregnancy. The increase in plasma volume and interstitial fluid, as well as increase in red cell mass would be expected to decrease the cyclosporine levels at a given dose. Because there is a greater increase in plasma volume than in red cell mass, a greater portion of any increase in cyclosporine dose would be distributed in the plasma and less would be red cell bound. It is not known whether sex steroids might slow the metabolism of cyclosporine through their inhibition of hepatic microsomes [125].

Although predictions about the effect of cyclosporine suggest forces working in opposite directions, the clinical observation is that cyclosporine levels drop and an increase in dose may be required to maintain the same plasma levels.

The most striking finding in transplant recipients treated with cyclosporine compared to those treated with other immunosuppressive regimens is an increase in SGA babies. The American Registry for Pregnancy in Transplant Recipients noted a low birth weight (< 2500 g) in 49.5% and a very low birth weight (< 1500 g) in 17.8% of 107 infants born to mothers treated with cyclosporine [126] during pregnancy. The frequency of low and very low birth weight for 207 infants born to mothers treated with prednisone and azathioprine was 39.1% and 7.7% respectively. The difference in gestational age was not significant (35.6 vs. 36.2 weeks.)

There was a higher frequency of maternal comorbid conditions in women treated with cyclosporine; 51.7% of cyclosporine-treated women were hypertensive prior to conception

compared to 18.5% of women treated with other regimens. More women in the cyclosporine-treated group had prepregnancy serum creatinine > 1.5 mg/dL (23.6% vs. 14.3%). It is not known whether hypertension and renal insufficiency before pregnancy account for the increase in IUGR.

The use of cyclosporine raises the question of its effect on the renal response to pregnancy in a renal transplant recipient. In transplant recipients treated with prednisone and azathioprine who have good renal function prior to conception (serum creatinine < 1.3 mg/dL), GFR, as measured by creatinine and inulin clearance, increases by a third by the tenth week of gestation and remains at an increased level until the third trimester when it returns to baseline [127]. The increase in GFR is less in women with lower prepregnancy GFR. It has not been determined whether cyclosporine, either by a direct effect or by virtue of the higher prepregnancy serum creatinine in cyclosporine-treated women, interferes with this response to pregnancy.

Experience with tacrolimus (FK 506) in pregnancy is extremely limited. It crosses the placenta and dose adjustment does not appear to be required for pregnancy. Severe IUGR was observed in one infant exposed to tacrolimus [128]. In one study of 9 pregnancies, hyperkalemia was seen in 5/ 7 surviving infants and one infant was anuric for 36 hours [129]. A recent report of 25 infants born to liver transplant recipients did not find IUGR, however neonatal hyperkalemia and renal insufficiency occurred [130]. Experience with the use of mycophenolate mofetil in pregnancy is even more limited.

Long-term survival of infants whose mothers were treated with cyclosporine during pregnancy is no different than for infants whose mothers were treated with azathioprine and prednisone alone. At present, taking cyclosporine out of the regimen is not warranted. Unless there is a clear indication for using tacrolimus or mycophenolate mofetil, the better studied combination of cyclosporine, azathioprine, and prednisone is preferable.

Pregnancy in Dialysis Patients

Fertility is decreased in dialysis patients. The American Registry for Pregnancy in Dialysis Patients reports a frequency of conception of 0.5% per year in women under the age of 44. For unclear reasons, conception is two to three times more common in hemodialysis patients than in peritoneal dialysis patients [89]. In 1980, the European Dialysis and Transplant Association reported on 115 pregnancies in women on dialysis [131]. Twenty-three percent of pregnancies not electively terminated resulted in surviving infants. The outcome was somewhat better in 344 pregnancies reported by the American Registry for Pregnancy in Dialysis Patients [89]. In the 187 pregnancies not electively terminated occurring in women receiving dialysis at conception, the likelihood of a surviving infant was about 40%. In contrast, the prognosis for the 59 pregnancies in women who began dialysis during gestation was better, with a fetal survival of approximately 70%.

Both hemodialysis and peritoneal dialysis have been used during pregnancy. There is no advantage of one modality over the other, either in fetal survival or in degree of prematurity.

When hemodialysis is used, it is common practice to increase the intensity of dialysis, based on the observation that women with residual renal function have a better outcome than women with no residual renal function. There is a suggestion of increased survival and less prematurity in pregnancies where the mother was dialyzed ≥ 20 hours per week [89].

Technical problems are not markedly increased with peritoneal dialysis, and catheters can be placed at any time during pregnancy. In the third trimester, abdominal discomfort usually makes it necessary to decrease exchange volume. There are few data on the effects of peritonitis on pregnancy outcome.

A substantial percentage of fetal loss occurs late in pregnancy, with 16.5% of pregnancies ending in second trimester spontaneous abortion and 6.4% in stillbirth. Of live-born infants, 18.2% die in the neonatal period, mostly from complications of prematurity. Little long-term follow-up is available on the surviving infants, but 11 of 49 infants where follow-up was available had developmental problems [89].

The frequency of complications is high, with > 75% of women suffering from hypertension, often severe. A drop in hematocrit is almost inevitable unless erythropoietin doses are increased 2 – 4 fold early in pregnancy. Almost all women not treated with erythropoietin require transfusion [89]. Two maternal deaths have been reported.

Acute Renal Failure (ARF)

ARF in pregnancy is largely a preventable problem resulting from obstetric complications and not intrinsic renal disease. Pregnancy-related ARF can thus be viewed more as a public health problem than a nephrologic problem. Historically, ARF in pregnancy once represented 20 – 40% of all cases of ARF and was responsible for 50% of cases in women [132]. In 1958, the estimated incidence of ARF in pregnancy was as high as 1 in 1400. Today, in industrialized countries, the approximate incidence is 1 in 20,000 [133]. In pregnancy, ARF occurs with a bimodal distribution. A peak in early pregnancy is associated with septic abortion, while a third trimester peak is associated with late obstetric complications, such as preeclampsia, abruptio placentae, postpartum hemorrhage, amniotic fluid embolism, and retained dead fetus [134, 135].

In industrialized countries where most women have access to high-quality prenatal care and where abortion has been legalized, there has been a marked decline in pregnancy-related ARF, with near elimination of the first peak [133]. The legalization of abortion in France was followed by a decrease in the percentage of cases of ARF attributable to obstetric causes, from 40% in 1966 to 4.5% in 1978 [133]. When abortion was made illegal in Romania in 1966, complications of illegal abortion became a major cause of ARF. In a report of 653 patients dialyzed for ARF between 1966 and 1989, 131 cases (20%) ARF resulted from complications of illegal abortion [136]. Between 1990 and 1992 after legalization of abortion, obstetric ARF accounted for only 1.52% of the total.

In developing countries, obstetric ARF remains a serious problem. Randeree et al. described the changing picture of obstetric ARF as the health care system in South Africa improved [137]. Between 1978 and 1991, the frequency of ARF in a hospital serving an impoverished community fell from one in 450 pregnancies to one in 900 pregnancies. With improvement in prenatal care, the proportion of obstetric ARF secondary to septic abortion decreased from 65% to 19%, while the percentage of obstetric ARF from preeclampsia increased from 10% in 1978 to 48% in 1991. With further improvement in obstetric care and early recognition of preeclampsia, the frequency of ARF from this cause would be expected to decrease.

ARF can occur after postabortal sepsis from any organism but is most common and dramatic with infection by *Clostridium welchii*, which produces a toxin that causes hemolysis and renal failure [138]. The infection may follow a fulminant course, characterized by severe abdominal pain and vascular collapse. *Clostridium welchii* is difficult to culture, and clostridia species are part of normal vaginal flora, but characteristic gas in the uterine wall on x-ray is highly suggestive. Care is supportive and is aimed at fluid resuscitation and infection control. The need for hysterectomy has been debated but can often be avoided with early aggressive conservative treatment [139, 140].

ARF in the Third Trimester

Bilateral Cortical Necrosis

In a majority of instances, ARF secondary to preeclampsia or peripartum hemorrhage follows a course typical of ATN with recovery. In obstetric ARF, a substantial minority of patients develop bilateral cortical necrosis, in which renal function may fail to recover or recovery may be partial with later progression to ESRD. Bilateral cortical necrosis may occur in any type of ischemic ARF, but a disproportionate number of cases occur in obstetric patients. In a report of 38 instances of cortical necrosis that occurred at Necker Hospital between 1953 and 1972, obstetric patients accounted for 26 (68%) [141]. The incidence of cortical necrosis was 2% in the nonpregnant adults with ARF and 21% of obstetric patients with ARF. There may be a vulnerability of the renal vasculature which is peculiar to pregnancy. It is notable that the Schwartman reaction can be induced in pregnant animals after one exposure to endotoxin, whereas nonpregnant animals develop it only after a second exposure [142]. Cortical necrosis can be diagnosed by CT scan or angiography [143]. The diagnosis is made primarily for prognostic purposes.

ARF in Preeclampsia

Decreased GFR, renal blood flow and sodium excretion are characteristic of preeclampsia, but frank renal failure is unusual. ARF in preeclamptic women occurs most often when another obstetric complication such as abruptio placentae is present, or when preeclampsia has progressed to the HELLP syndrome [144 – 146]. In the largest series of patients with HELLP, 7.7% suffered ARF. In one report of 17 preeclamptic women with ARF, 80% of women who developed cortical necrosis had abruptio placentae compared to one third of those who recovered renal function [145]. When ARF follows preeclampsia, there is substantial risk of maternal mortality (9.6% in one study) [144]. Pulmonary edema occurs in > 50% of women with ARF secondary to preeclampsia, emphasizing the need for judicious fluid administration in women with preeclampsia. Women who survive ARF in the setting of preeclampsia without essential hypertension or underlying renal disease have normal renal function at long-term follow-up. When ARF occurs in women with underlying chronic renal disease and renal insufficiency, as many as 80% are dialysis dependent at follow-up [144]. In these women, it is frequently difficult to distinguish between ARF secondary to preeclampsia and the poorly understood acceleration of renal failure in women with preexisting renal insufficiency, particularly because these women are frequently hypertensive when they lose renal function.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is an obstetric emergency. If left untreated, it may progress to fulminant hepatic failure which is life threatening for both mother and fetus. The disease most often presents in the third trimester, with complaints of headache, fatigue, malaise, nausea, and abdominal pain. Late signs include jaundice, bleeding, seizures, and hepatic encephalopathy that may progress to frank coma. Liver biopsy shows microvesicular fatty infiltration of hepatocytes in a centrilobular distribution [147]. The maternal mortality rate for the disease has improved from 80 – 85% in the 1970s to less than 20% in recent series, with the lowest mortality rate reported being 6.6% [148 – 150]. The improvement in outcome can be attributed to earlier recognition and treatment, the recognition of milder cases, and better supportive care of fulminant hepatic failure. Acute fatty liver is frequently accompanied by preeclampsia, and there may be a link between the 2 syndromes. The etiology of the syndrome is unknown, but recent investigations have found a familial metabolic defect in fatty acid metabolism [151 – 153].

Some degree of ARF occurs in up to 90% of women with acute fatty liver of pregnancy [148, 149]. Renal biopsy findings in acute fatty liver of pregnancy include ATN, fatty vacuolization of tubular cells, and occlusion of capillary lumens by fibrin-like material. Clinically, the ARF in this syndrome may resemble hepatorenal syndrome, with low fractional excretion of sodium (FE_{NA}) and benign sediment. Treatment includes delivery of the baby and supportive care. ARF usually resolves postpartum, as does the liver failure. The availability of orthotopic liver transplant offers a life-saving treatment to women who do not recover postpartum. The timing of liver transplant is difficult. Waiting may result in the patients' deterioration and increase transplantion mortality. A transplant done prematurely may commit a woman to life-long immunosuppression when she might have had a complete recovery.

Postpartum Hemolytic Uremic Syndrome (HUS)

Initially described in children with antecedent diarrheal illness and in association with verotoxin, HUS is characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. It is also recognized in adults in association with diarrheal illnesses, certain forms of adenocarcinoma, medications, and pregnancy. Early reports of postpartum HUS refer to the syndrome as postpartum renal failure. Although it usually occurs between one day and 3 months postpartum, HUS may occur before delivery as well [154, 155]. Thrombotic thrombocytopenic purpura (TTP), considered to be related to HUS along a continuum, typically occurs during, but occasionally after pregnancy. Renal failure in both HUS and TTP is often severe enough to require temporary dialysis, and patients may suffer residual renal damage, some severe enough to require chronic dialysis or transplant [156].

In a review of 68 adults with HUS/TTP of various etiologies diagnosed between 1980 and 1982, Conlon found a normal urinalysis at presentation in only 3%. Eighty-six percent had microscopic hematuria and 89% had proteinuria [157]. In one study of 11 women with pregnancy-associated HUS, 81% had impaired renal function at presentation.

The mainstay of treatment for HUS/TTP is plasma exchange. Before the advent of plasmapheresis, the maternal mortality rate was 90%. With this treatment, maternal survival has increased to 70 – 80%. Plasma exchange

during pregnancy has not shown adverse effects on the fetus [158, 159]. It is thought to work by removing factors that promote platelet aggregation and replacing inhibitory factors that may be lacking in the serum of patients with HUS/TTP. The number of treatments necessary varies among patients, ranging from 5 – 47 days in one study of 67 women [160]. The duration of treatment is determined by monitoring hematologic, neurologic, and renal parameters. Other treatments have included prednisone, aspirin, dipyridamole, heparin, immunoglobulin, vincristine, and splenectomy. These should be considered only as adjuncts to plasma exchange.

Recurrence of HUS has been described both in subsequent pregnancies and in response to other inciting factors, including oral contraceptives, infections, and drugs such as cyclosporine.

It is sometimes difficult to distinguish between HUS/TTP and severe preeclampsia accompanied by the HELLP syndrome. Thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, proteinuria, and hypertension may occur in both. Some distinguishing features include isolated elevation of lactate dehydrogenase (LDH) in HUS/TTP, as opposed to elevation of transaminases in preeclampsia/HELLP. Elevations of PT and PTT are unusual in HUS/TTP and suggest preeclampsia. Preeclampsia generally improves after delivery, although there may be transient worsening for 48 hours. TTP/HUS is not improved by termination of pregnancy. The distinction is important because preeclampsia resolves with supportive care after delivery, but HUS/TTP is generally irreversible without plasma exchange.

Biopsy findings in HUS/TTP include glomerular capillary endothelial swelling and subendothelial deposition of fibrinoid material that may cause occlusion of capillaries [157]. Thrombi composed of fibrin and platelets are found within capillaries and arterioles [157].

The pathophysiology of microthrombus formation in HUS/TTP is thought to involve endothelial injury along with other factors contributing to enhancement of platelet aggregation or a decrease in inhibitors to platelet aggregation. Among those factors, abnormally large multimers of von Willebrand factor have been observed in TTP, and these can cause aggregation of activated platelets. Calpain, a cysteine protease capable of causing aggregation of normal platelets and enhancing platelet binding by von Willebrand factor, has been found in some patients with active TTP. Decreased fibrinolysis may play a role. Plasminogen activator inhibitor type 1, the major inhibitor of plasminogen activator, is increased in some cases of postdiarrheal HUS. Decreased synthesis and increased degradation of prostacyclin have been suggested on the basis of studies using plasma from individuals with TTP [161]. There may also be some genetic predisposition to HUS/TTP. There are known familial occurrences, and pregnancy-associated HUS has been reported in sisters [162 – 164].

Although advances in treatment have dramatically increased patient survival in obstetric HUS/TTP, it still poses a significant threat to both mother and child, particularly if not diagnosed and treated promptly. Patients with pregnancy-associated HUS/TTP should be aware of the possibility of recurrence in future pregnancies and with estrogen-containing oral contraceptives, although at present there is no method to identify those who will be affected a second time.

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Appendix

Food and Drug Administration categories evaluating the risk of drugs to the fetus.

A. Controlled studies fail to demonstrate risk to the fetus even in the first trimester and the possibility of fetal harm appears remote.

B. Either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).

C. Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or others) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may justify the risk.

X. Studies in animals or human beings have demonstrated fetal abnormalities, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Tubulointerstitial and Vascular Diseases

Georg M. Fiedler, Volker Becker and Gerhard A. Müller

Tubulointerstitial Nephritis

Mechanisms of Tubulointerstitial Nephritis

The tubulointerstitial compartment accounts for 80% of the renal mass [1]. It consists of renal tubuli, the tubular basement membrane, vascular structures, and interstitial cells as well as the surrounding extracellular matrix. The interstitial cells can be divided mainly into renal fibroblast cells and cells of the monocyte/macrophage system including dendritic cells [1]. The tubulointerstitial compartment is involved in the course of almost all renal diseases [2]. As a rule, changes begin with an interstitial inflammation that is the hallmark of tubulointerstitial nephritis (TIN). TIN can exist in an acute and a chronic form and can affect the tubulointerstitial space primarily or in the setting of primary glomerular or vascular diseases. All forms of interstitial disease are quite common. It has been estimated that up to 15% of all cases of acute renal failure (ARF) are caused by primary interstitial nephritis [3]. In addition, up to 25% of all cases of end-stage renal disease (ESRD) are attributable to primary chronic TIN [4]. According to the European Dialysis and Transplant Association (EDTA) registry, 20.2% of ESRD was caused either by pyelonephritis, interstitial nephritis, or toxic nephropathy. These forms are characterized by primary TIN [5]. More recent data, however, suggest a less prominent role, with about 4.5% of cases of chronic renal failure (CRF) in the US attributable to primary interstitial diseases [6]. Moreover, secondary tubulointerstitial injury is one of the most important factors for the outcome of primary glomerular and vascular diseases [7] because interstitial nephritis is the common pathway of almost all forms of progressive renal disease and one of the most common lesions in nephrology [8]. Immune response in interstitial nephritis can be antibody dependent or cell mediated but, in contrast to glomerular diseases, cell-mediated reactions predominate [9].

In TIN, T lymphocytes are the predominant infiltrating cells with a great abundance of CD4+ T helper cells (CD4/CD8-ratio often > 1). These T helper cells need MHC-class II (HLA-D) restricted presentation of responsible antigens to become activated. Antigen presentation in the renal interstitium can be provided efficiently by infiltrating macrophages and interstitial dendritic cells [10]. In addition, data on glomerular diseases suggest that tubular epithelial cells may serve as antigen presenters as well [11]. In interstitial nephritis, predominantly CD8+ T effector cells become activated in turn and result in renal tissue damage by 2 mechanisms: they can be cytotoxic due to the release of perforans, or they can lead to a delayed-type hypersensitivity reaction with the release of inflammatory

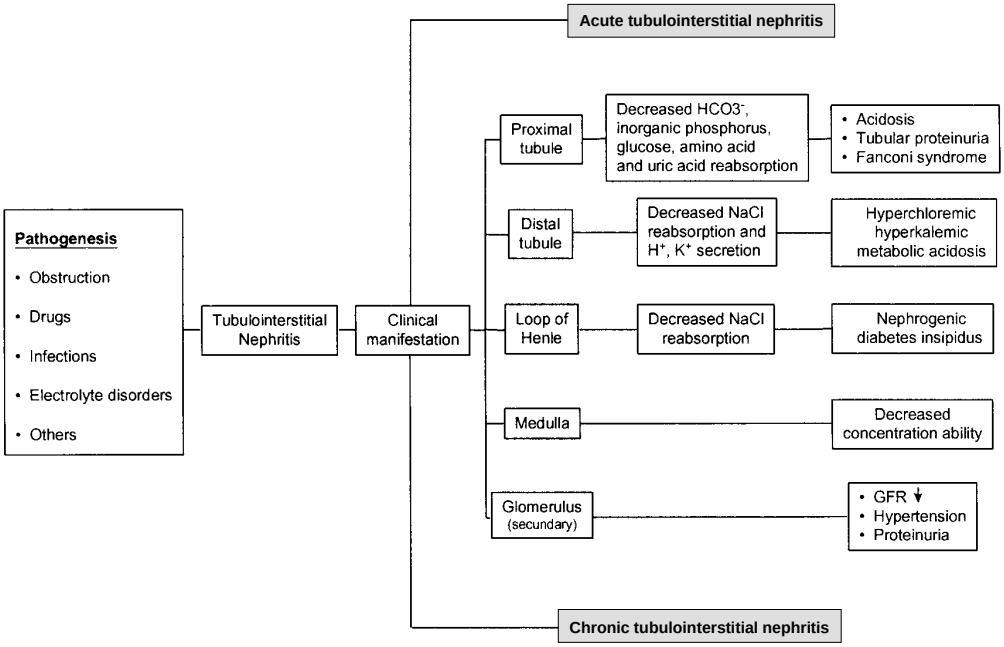

Figure 1. Pathogenesis and clinical manifestations of tubulointerstitial nephritis. Modified from [Kuhlmann U., Walb D, Luft FC: Nephrologie. 3rd ed., Thieme, Stuttgart 1998] with permission.

cytokines [12]. Only occasionally, deposition of immune complexes within the interstitium may be found, especially in patients with underlying systemic autoimmune disorders. In rare cases of specific antitubular basement membrane disease, linear deposition of immunoglobulin along the tubular basement membrane can be detected (additionally in up to 70% of cases with primary antiglomerular basement membrane (anti-GBM) disease). The target antigens for humoral immunity in human TIN remain poorly defined [13, 14]. Only the target antigen of experimental antitubular basement membrane (TBM) disease in mice has been characterized as glycoprotein 3M-1 and is secreted by proximal tubular cells [15, 16]. Apart from native renal antigens, drug/hapten conjugates, microbial antigens, and foreign antigens that induce cross-reactive immunity to autoantigens (molecular mimicry) are believed to be of importance in TIN. Irrespective of the type of immune reaction, in the course of sustained primary or secondary interstitial inflammation and tissue damage, activation of interstitial cells can initiate processes of interstitial proliferation and fibrogenesis that inevitably result in renal scarring and chronic renal failure.

Figure 1 summarizes the pathogenesis and clinical manifestations of TIN.

Acute Tubulointerstitial Nephritis (ATIN)

ATIN is a heterogeneous disorder in etiology, clinical presentation, laboratory findings, and outcomes. The incidence of ATIN for cases of clinically encountered ARF is diffi-

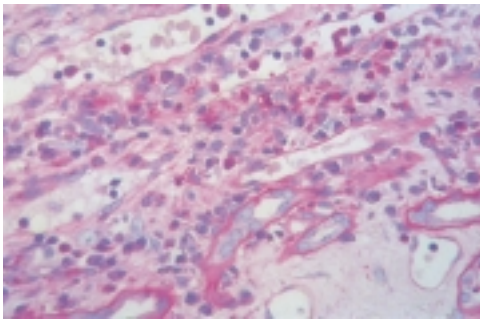

Figure 2. Acute drug-induced tubulointerstitial nephritis (ibuprofen) in a 60-year-old woman. Observe the dense lymph/plasma cell and eosinophil (characterized by their dark cytoplasm) infiltration (PAS, magnification x 400).

cult to establish. It has been estimated that up to 15% of all cases of ARF are caused by primary interstitial nephritis [3, 8]. The proportion of CRF attributable to ATIN is fortunately much lower, in the range of 1‰. ATIN is slightly more common among men than in women (about 2 – 3 : 1) and can be observed in any age. Elderly patients are more often affected, however, probably because of the more abundant use of drugs in this group.

Pathology

The principal morphologic changes that characterize all forms of ATIN are interstitial expansion caused by edema and infiltration of inflammatory cells as well as pathological changes in the tubules. Usually, the glomeruli and renal vascular structures appear unaffected. The nature of the cellular infiltrate varies according to the underlying disease. In general, the infiltrating cell population is composed mainly of neutrophils, T and B lymphocytes, macrophages, natural killer (NK) cells, plasma cells, and eosinophils [9, 17 – 21] (Figure 2). The infiltrate is typically T lymphocytes and monocytes/macrophages [22] in interstitial nephritis associated with glomerular disease. The interstitial infiltrates are often diffuse, but focal patterns of injury are also seen. Granuloma formations may be found as well, and drugs are a common cause of these lesions in acute settings [23 – 25]. However sarcoidosis, granulomatous vasculitis, or tuberculosis should be considered in such cases [24, 26 – 28]. In cases of Wegener granulomatosis, glomerular and vascular structures are almost always involved [27]. The tubular changes range from cell swelling and vacuolization to tubular cell necrosis with disruption of the tubular basement membrane [20]. A marked expression of adhesion- and HLA-class-II molecules by tubular cells can be observed by immunohistochemistry and may be of great importance for the disease process [19, 29, 30]. In contrast to glomerular diseases, deposition of immunoglobulins or complement are of minor importance [17].

Clinical Features

In ATIN, a rapid decrease in renal function is typical at presentation. A careful evaluation of the history is essential in this setting because most patients will be asymptomatic or will complain only of unspecific symptoms. For example, the clinician should be on the alert for a new medication, especially in the elderly patient, or systemic illness, particularly streptococcal infections in children. While there are no pathognomonic clinical findings in ATIN, certain systemic manifestations may point to the diagnosis if present. The classical descriptions of patients with methicillin-induced interstitial nephritis go back to the early 1960s. Systemic manifestations such as

- low-grade fever (70 – 100%),
- fleeting skin rash (30 – 50%), and
- diffuse arthralgias (up to 20%)

Table 1. Laboratory Features of ATIN

Blood	Eosinophilia IgE-Elevation
Proteinuria	< 3 g/day (exception: some cases of NSAID) Tubular pattern (α1-microglobulin, β2-microglobulin, N-acetyl-beta-glucosaminidase)
Sediment	White blood cells (free and casts) Microhematuria (rarely gross hematuria, red casts uncommon) Eosinophiluria
Functional parameters	Glucosuria, aminoaciduria, hyperphosphaturia Renal tubular acidosis (bicarbonate loss, impaired acid secretion) Hyperkalemia Salt wasting Impaired concentration ability

together with signs of ARF make ATIN a probable diagnosis [31].

However, the entire constellation has been reported in the minority of ATIN cases (4 out of 27 in one study) [32]. In most cases only nonspecific constitutional symptoms such as fever, fatigue, or nausea are present. In addition, some patients may complain of lumbar pain due to distension of the renal capsule from diffuse swelling of the kidney. In contrast to glomerular diseases, oliguria, edema, and hypertension are less common in ATIN. As a consequence of an impaired tubular reabsorptive capacity, polyuria and nocturia may develop. Long-term consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to a type of ATIN, accompanied by glomerular proteinuria sometimes severe enough to cause full-blown nephrotic syndrome. ATIN histologically characterized by granuloma formation within the interstitium can clinically appear months after drug ingestion. Typically, classic allergic symptoms are lacking. Therefore, diagnosis is often delayed in these cases, and progression to renal failure often occurs.

Laboratory Findings

The first clinical presentation of ATIN is variable, and specific findings that point to diagnosis are often lacking. Several findings on blood and especially urine analysis may point of ATIN (Table 1). Elevated plasma creatinine and blood urea nitrogen (BUN) values should be investigated to discover the cause of impaired renal function. Especially in drug-related ATIN, further blood tests may reveal transient eosinophilia and elevated plasma IgE levels, but these findings occur only in about 30% of cases [33 – 35]. In addition, nonspecific elevations of C-reactive protein (CRP) levels and an accelerated erythrocyte sedimentation rate (ESR) may be present. In > 75% of cases, mild to moderate proteinuria and hematuria can be found [36, 37]. Proteinuria is tubular in the majority of cases. Nephrotic-range proteinuria is not usually found. However, NSAID-induced interstitial nephritis is often characterized by serious renal injury including the glomeruli (minimal change lesions). Hence, this form of ATIN may be accompanied by nephrotic syn-

drome [38]. Gross hematuria rarely occurs in ATIN, but careful examination of the urinary sediment is essential. In approximately 75% of patients, red and white blood cells (sterile pyuria) will be found [37]. Occasionally, white and red blood cell casts may be observed, but the latter strongly suggest a glomerular lesion. Eosinophiluria is suggestive of allergic interstitial nephritis. Eosinophils in the urine can be detected by either Wright's stain or Hansel's stain, the latter being approximately 5 times more sensitive [39, 40]. However, eosinophiluria can be observed in many other cases such as rapid progressive glomerulonephritis (GN), urinary tract infections (UTI), prostatitis, and atheroembolic disease, as well as in episodes of renal allograft rejection. Therefore, it may help to distinguish ATIN from acute tubular necrosis (ATN), but the positive predictive value of this parameter is < 40% according to recent studies [41].

As a consequence of tubular injury and interstitial inflammation, various tubular dysfunctions may be observed in the course of ATIN. Lesions affecting the proximal tubule may result in glucosuria, aminoaciduria, uricosuria, and hyperphosphaturia. A proximal loss of bicarbonate along with an impaired acid secretion within the distal segments can result in renal tubular acidosis. Hyperkalemia and renal salt wasting together with a reduction of renal concentration ability may point to a dysfunction of the distal tubule or collecting duct. In a report of 9 patients with biopsy-proven ATIN, isosthenuria was present in all patients with a mean urinary osmolality < 350 mOsm/L and a urine/plasma osmolality ratio of 0.9. Urinary sodium was > 40 mEq/L in 8 out of the 9 patients studied [42]. However, signs of tubule dysfunction such as Fanconi syndrome and renal tubular acidosis are rarely observed in the course of ATIN and are more common in patients with chronic tubulointerstitial disease.

Table 2. Etiological Factors of ATIN

Drugs
Infections
Idiopathic
Associated with Uveitis (TINU-Syndrome)

Diagnosis

Tubulointerstitial nephritis is a pathological phenomenon and not a clinical syndrome. Many features in clinical presentation and in laboratory analysis may suggest ATIN but only renal biopsy can establish the diagnosis with certainty in this setting. Therefore, renal biopsy should always be considered in any patients with ARF of unknown origin.

Ultrasonography is useful in the detection of ATIN. Because of the increased interstitial volume, the kidneys may appear swollen and the cortical echogenicity may be increased. Additionally, renal scanning with gallium-67 has also been reported to detect ATIN in some patients [35, 43]. This method is very sensitive; however, the specificity is relatively low. Therefore, this method is not reliable in identifying noninfectious interstitial nephritis [44].

Etiology

The etiological factors that can lead to acute interstitial nephritis may be divided into 3 categories (Table 2). Drugs are the most im-

Table 3. Drugs Causing ATIN

Antibiotics	*Diuretics*
Penicillins and derivatives	Thiazides
Cephalosporins	Triamterene
Azithromycin	Hydrochlorothiazide/ Amiloride
Chloramphenicol	Furosemide
Ciprofloxacin	Indapamide
Erythromycin	Chlorthalidone
Ethambutol	
Minocycline	*Miscellaneous*
Nitrofurantoin	Allopurinol
Polymyxin B	Azathioprine
Rifampicin	Captopril
Rolitetracycline	Carbamazepine
Spiramycine	Clofibrate
Sulfonamides	Interferon α
Tetracyclines	Interleukin-2
Trimethoprim-sulfamethoxazole	Paracetamol
Vancomycin	Phenindione
Acyclovir	Phenobarbital
Foscarnet	Phenytoin
Griseofulvin	Propylthiouracil
	Streptokinase
Nonsteroidal anti-inflammatory drugs	Sulfinpyrazone
	Ticlopidine
	Triazolam
	Warfarin
Anti-ulcer-medications	Anti-CD4 antibody
Omeprazole	Hairy vetch poisoning
Ranitidine	
Cimetidine	

Table 4. Infections Causing ATIN

Bacteria	*Viruses*
Brucella species	Epstein-Barr virus
Campylobacter	Cytomegalovirus
Corynebacterium diphtheriae	Hanta virus
Escherichia coli	Hepatitis B virus
Legionella pneumophila	Herpes simplex virus
Pseudomonas aeruginosa	HIV
Salmonella	Rubeola
Serratia marcescens	Polyomavirus
Streptococcus	
Staphylococcus	
Yersinia	
Others	
Histoplasmosis	*Mycoplasma hominis*
Leptospira	*Rickettsia rickettsii*
Leishmania donovani	*Schistosoma mekongi*
Mycobacterium tuberculosis	*Toxoplasma gondii*

portant causative agents, followed by systemic infections, particularly in children. Less common are autoimmune and systemic disorders or idiopathic origin [22].

Drugs

With the introduction of sulfonamides in the 1940s, an association of nephritis with these substances was recognized. Classical reports of drug-induced ATIN are those with maculopapular rash, fever, and eosinophilia after the ingestion of methicillin [45 – 47]. Hence, most studies were performed on β-lactam antibiotics in the past. Currently, quinolones and proton pump inhibitors are the leading causative agents, followed by 5-aminosalicylate and NSAIDs. As drug-related ATIN seems to be due to a hypersensitivity reaction, it can be induced by virtually any drug. However, certain drugs are more prone to induce ATIN (Table 3).

Drug-induced ATIN may occur in a variety of forms (Figure 3). Depending on the drug involved and the individual response, the clinical symptoms can range from full-blown hypersensitivity (fever, rash, eosinophilia, and oliguric renal failure) to asymptomatic courses with only laboratory findings. Altogether, drug-induced ATIN should always be considered in patients with an abrupt deterioration of renal function and signs of tubular dysfunction.

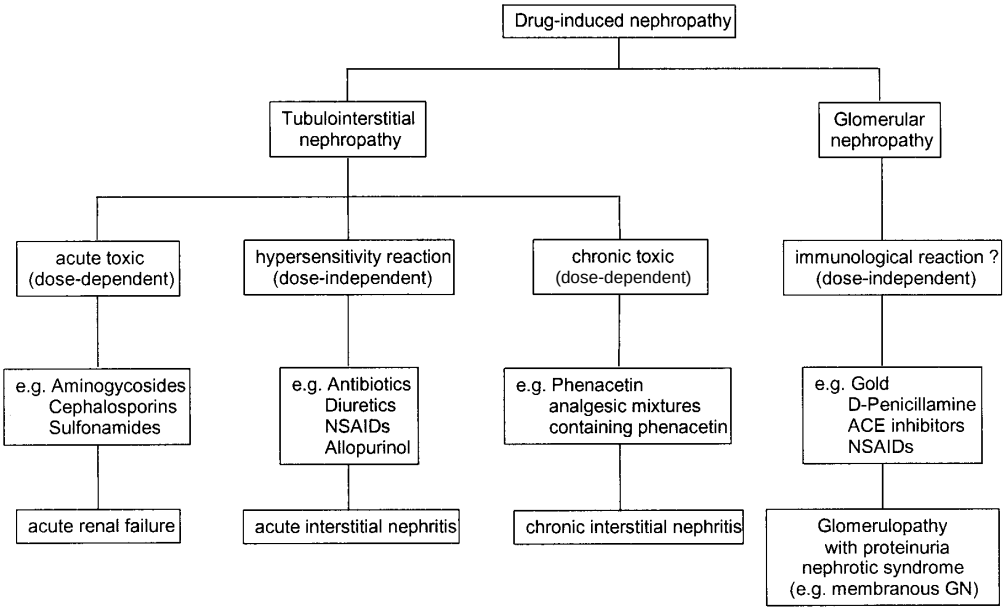

Figure 3. Drug-induced nephropathy. Modified from [Kuhlmann U., Walb D, Luft FC: Nephrologie. 3rd ed., Thieme, Stuttgart 1998] with permission

Infections

Infection-mediated ATIN (Table 4) is usually caused by an ascending infection with *Enterobacteriacae* (most commonly *E. coli*) and *Streptococcus faecalis*. In hospitalized patients, UTIs with other organisms such as *Serratia marcescens* or *Pseudomonas aeruginosa* are more common due to exposure to these bacteria and concurrent antibiotic treatment. Tubulointerstitial infections are dependent on the presence of urinary reflux and on bacterial virulence factors. Because of its high prevalence, the most extensively studied pathogen is *E. coli* [48]. One virulence factor that seems to be very important is the presence of fimbriae that enable the bacterium to adhere to epithelial cells [49]. P-fimbriae play an important role in first attacks of pyelonephritis due to their capability to mediate adhesion to human P blood group receptors [49]. Thus, although only 10 – 15% of all *E. coli* strains that cause UTI are P-fimbriated, 70 – 100% of all cases of nonobstructive pyelonephritis are caused by P-fimbriated *E. coli*. Another potential virulence factor is the presence of α-hemolysine [50]. The importance of all virulence factors seems to be linked to their neutrophil activation ability [48]. Polymorphonuclear neutrophils (PMN) may directly activate fibroblasts and thus cause interstitial fibrosis. However, experimental data to support this hypothesis are still lacking. Nevertheless, direct interaction of PMNs and fibroblasts has recently been demonstrated [51]. The role of lymphocytes and cytokines in acute and chronic phases of infection is not as well defined as in other forms of TIN. Nevertheless, it is known that even in infectious TIN T lymphocytes accumulate within a few days [52]. CD4+ from lesions in experimental pyelonephritis displayed MHC-restricted proliferative responses to a variety of *E. coli* and related strains, but not to other gram-negative bacteria [52]. Thus, it seems possible that many forms of chronic infec-

tious TIN are mediated by the same immune mechanisms as noninfectious forms. Cytokines that play a role in infectious TIN include interleukins IL-1 and IL-6, granulocyte-colony stimulating factor (G-CSF), granulocyte-monocyte-colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF)-α according to a study by Rugo et al. [53]. The role of obstruction itself is often underappreciated. Obstruction, albeit often the cause of chronic infection, can lead directly to tubulointerstitial injury. An increase in fibrogenic cytokines has been demonstrated in models of ureteral obstruction. For example, Kaneto et al. demonstrated increased transforming growth factor (TGF)-β1 mRNA expression in the tubules of rats with unilateral ureteral obstruction [54]. Moreover, sterile urine reflux caused cortical tubulointerstitial scarring in pigs [55], a mechanism potentially initiated by the extravasation of Tamm-Horsfall glycoprotein at high backflow pressures [56]. Another form of ATIN is observed in systemic infections in which there is no evidence of direct parenchymal invasion by an organism. However, the pathogenesis of this entity is unknown.

Idiopathic ATIN

In a proportion of cases, no etiological factors can be identified. This form of ATIN cannot be distinguished from other forms by any specific symptoms or other characteristic findings [57]. In most cases it is reversible. Pathologically, mononuclear cells predominate within the interstitium. However, the resulting lesions are heterogeneous and occasionally, as with other clinical settings, anti-TBM-antibodies can be found. Thus, the idiopathic form(s) of ATIN can only be distinguished from other forms by exclusion of infections, history of drug ingestion, or immune disorders.

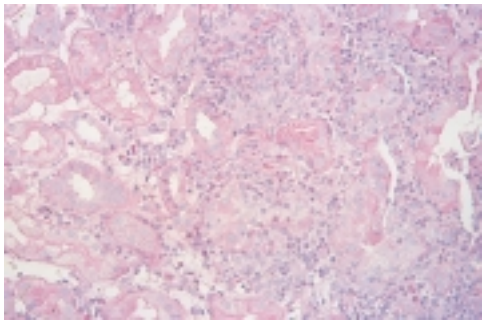

Figure 4. Tubulointerstitial nephritis in a 17-year-old girl with TINU syndrome. The interstitium shows dense lymph/plasma cell infiltration with focal tubulitis. Some eosinophils are scattered in between (PAS, magnification x 200).

The association of acute tubulointerstitial nephritis and acute uveitis observed in several patients (in adolescent girls or occasionally in adults) has led to the identification of a specific syndrome with a very particular symptomatology and course, the so-called tubulointerstitial nephritis/uveitis (TINU; Figure 4). The etiology of TINU syndrome remains to be elucidated but a recent report suggests underlying infection with *Chlamydia*. The prognosis of TINU seems to be excellent in younger patients, with or without steroid treatment. In adults, however, CRF ensues in a substantial proportion [58, 59, 60].

Course and Treatment

The clinical spectrum of ATIN ranges from mild and short to severe cases with oliguric renal insufficiency. The primary therapeutic step in ATIN is to identify and withdraw the drug or offending agent, or to treat the underlying infection. Most patients will recover fully from renal failure within several days. In cases of ongoing and progressive renal insufficiency, a kidney biopsy should be performed to exclude other diseases (e.g. myeloma kidney, rapid progressive glomerulonephritis, or atheroembolism).

Although corticosteroids have been reported to be beneficial in some patients [31, 61], controlled clinical trials are not yet available. In the absence of a prompt response after withdrawal of a drug or offending agent, Kelly and Neilson suggest a trial of corticosteroids (1 mg/kg/day prednisone) in patients without infection. Improvement in renal function should begin within 1 – 2 weeks of initiation of treatment, in which case the course can be discontinued after 4 – 6 weeks [62]. If no improvement is seen within the first 2 weeks, an additional therapy with cyclophosphamide (2 mg/kg/day) with appropriate monitoring of the white blood cell count should be considered [62]. If successful, this regimen should be continued up to one year. When no evidence of improvement exists after 6 weeks, the combined therapy should be discontinued [62].

Most patients will have complete recovery of renal function within one year. However, up to one-third of patients with drug-induced acute interstitial nephritis (and more in the case of rifampicin) require dialysis treatment before resolution of the disease [62].

Chronic Tubulointerstitial Nephritis (CTIN)

Pathology

The pathological findings in patients with chronic forms of tubulointerstitial nephritis display characteristic changes in interstitial architecture observed in virtually all forms of chronic renal injury, e.g. of primary glomerular, vascular, cystic, or interstitial origin [7, 21]. Interstitial fibrosis along with tubular atrophy are the hallmarks of chronic interstitial disease. As an expression of ongoing inflammation, mononuclear cell infiltrates

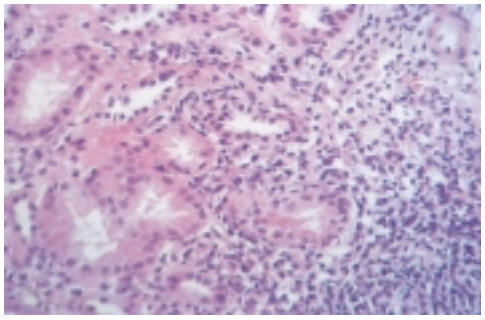

Figure 5. Secondary tubulointerstitial nephritis in Sjögren's syndrome, 68-year-old woman. Focally dense lymph/plasma cell infiltration (PAS, magnification x 400).

(mainly lymphocytes) in the interstitium and within the tubular epithelium (tubulitis with resulting cellular casts) can be seen (Figure 5). Although in CTIN the glomeruli mainly remain unaffected by the primary lesion, signs of secondary glomerular injury may be found as the disease progresses towards ESRD [10, 19, 63 – 65].

Clinical Features

Usually, CTIN does not cause any specific clinical symptoms unless a primary systemic disease is present. Hence, some cases are diagnosed because of findings in screening tests (abnormal urinalysis or elevations in plasma creatinine and BUN). However, many patients unfortunately present with nonspecific symptoms of chronic renal failure late in the course of the disease [66].

Laboratory Findings

When patients with CTIN present late, they have marked impairment of renal function and typical laboratory findings of chronic renal failure. Earlier cases of CTIN may present

with nonnephrotic-range proteinuria of a predominant tubular protein pattern and microscopic hematuria as well as pyuria. Surprisingly, positive urine cultures can be found in as many as 28% of patients [66]. As with acute TIN, glucosuria, renal tubular acidosis (RTA), and concentration defects reflect the degree of tubular dysfunction. Anemia develops relatively early (compared to glomerular diseases), and systemic hypertension occurs in about 50% of cases.

Diagnosis

Renal biopsy is the only means for definite diagnosis in all forms of TIN, whether acute or chronic. Neither clinical features nor laboratory findings are specific. In CTIN associated with a primary disease, diagnosis may be suggestive in many cases but biopsy is still of great value, especially for informed judgement on individual prognosis and required therapeutic decisions. Nevertheless, a thorough investigation of the patient's history will provide the only reasonable basis for diagnosis in many patients with established late-stage renal failure.

Etiologic Factors

CTIN can occur in association with a variety of underlying primary diseases of diverse etiology. Table 5 gives a concise overview of common and rare causes of CTIN, which are discussed in more detail in other chapters.

Endemic Nephropathy

Endemic nephropathy, so-called Balkan nephritis, is a form of CTIN that is endemic in areas of the Balkan states. Usually, the disease occurs in middle-aged adults and progresses slowly towards ESRD. No diagnostic tests are

Table 5. Causes of Chronic Tubulointerstitial Nephritis

Hereditary Diseases
Autosomal dominant polycystic kidney disease
Medullary cystic disease / Juvenile nephronophthisis
Metabolic Disorders
Hypercalcemia (nephrocalcinosis), Hypokalemia
Hyperuricemia
Hyperoxaluria / Cystinosis / Methylmalonic acidemia
Drugs and Toxins
Analgesics
Lithium
Cyclosporine
Cisplatin
Nitrosoureas
Chinese herbs
Cadmium / Lead
Germanium lactate citrate
Immune Mediated
Renal allograft rejection
Systemic lupus erythematosus
Wegener granulomatosis / Microscopic polyangiitis
Vasculitis (other)
Sjögren syndrome
Sarcoidosis
Hematologic Disorders
Multiple myeloma
Light chain deposition disease
Paroxysmal nocturnal hemoglobinuria
Lymphoma
Sickle cell disease
Obstructive Disorders
Tumors
Stones
Outlet obstruction
Vesicoureteral reflux
Infections
Direct infection
Malacoplakia
Xanthogranulomatous pyelonephritis
Miscellaneous
Endemic nephropathy
Radiation nephritis
Progressive glomerular disease
Primary biliary cirrhosis
Aging
Hypertension
Ischemia
Extracorporal shock wave lithotripsy

available, and its cause remains unknown (environmental agents, infections, and genetic factors are proposed). A higher incidence of uroepithelial tumors is suggested in these patients. As with other forms of TIN, elevated excretion of tubular proteins (especially β2-microglobulin) as well as additional signs of tubular dysfunction can be observed early in asymptomatic patients [67]. At this time there is no specific treatment regimen that can alter the rate of progression towards renal failure. Thus, elimination of known progression factors is essential.

Sarcoidosis (M. Boeck)

Most commonly, aberrations of calcium metabolism, including hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis, are responsible for the renal manifestations of sarcoidosis (Table 6). Recent studies suggest that the calcium abnormalities are associated with high blood concentrations of calcitriol and that calcitriol may be synthesized by mononuclear macrophages in the granulomas [68]. Up to one-third of patients with sarcoidosis are reported to have granulomas within the renal interstitium, which may also produce severe derangements of renal function. GN can occur with sarcoidosis, although the pathogenesis remains unclear [69 – 72].

Table 6. Renal Manifestation of Sarcoidosis

1. Disturbance of calcium metabolism
– Hypercalcemia and hypercalciuria
– Nephrolithiasis
– Nephrocalcinosis
2. Granulomatous tubulointerstitial nephritis
3. Different pattern of glomerular disease

Clinically apparent kidney dysfunction is rare unless hypercalcemia and hypercalciuria are present (about 10 – 15% of all patients). Mild to moderate albuminuria, microscopic hematuria, and sterile pyuria predominate. A protein excretion of > 3 g/24hours may indicate a concomitant glomerular lesion. Hypertension is usually absent and renal size is well preserved. Urinary concentration defects (including nephrogenic diabetes insipidus), renal tubular acidosis, and inappropriate glucosuria may also be seen [73]. In patients with sarcoidosis-associated granulomatous TIN, renal disease is usually accompanied by other organ involvement. No factors are known to identify patients at high risk, but men are reported to be more prone to develop this entity. The findings in renal biopsy are distinct from other forms of TIN. Interstitial inflammation with noncaseating granulomas and epithelioid and multinucleated giant cells is the usual histologic picture (Figures 6a and 6b). There is no positivity for complement or immunoglobulins. Rarely, nonspecific glomerular or vasculitic changes can be observed. Pathologically, other granulomatous inflammatory processes like silicosis, tuberculosis, histoplasmosis, and Wegener granulomatosis or scattered infiltration by lymphoma cells (with reactive granuloma formation) may have to be distinguished in single cases. Interestingly, in a series of 6 patients with sarcoidosis and clinically significant renal insufficiency, 4 patients differed from the typical patient with sarcoidosis in that they lacked the usual clinical constellation of skin, eye, and pulmonary involvement [71].

The diagnosis is supported by clinical findings of sarcoidosis involvement of other organs and should be suspected on the basis of elevated or paradoxically normal serum calcium concentrations, due to increased plasma concentrations of calcitriol, while immunoreactive circulating parathormone concentra-

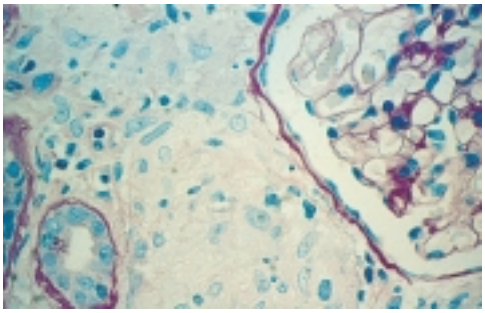

Figure 6a. Granulomatous interstitial nephritis in a 68-year-old man. Groups of histiocytes with one or more nuclei (PAS, magnification x 400).

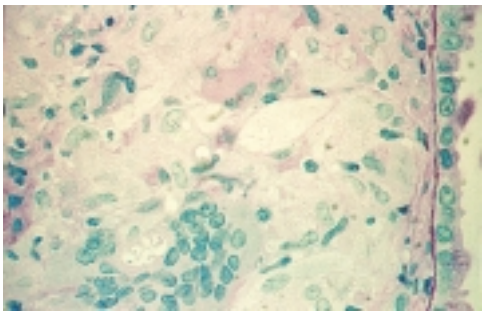

Figure 6b. Giant cell in the same patient (PAS, magnification x 400).

tions are depressed. An elevated 24-hour urine calcium concentration is consistent with the diagnosis but is not specific. Additionally, angiotensin-converting enzyme (ACE) activity is elevated in the serum in approximately two-thirds of patients with sarcoidosis. However, false-positive and false-negative results are common. Calcitriol as well as ACE could represent unregulated secretion products from granulomatous tissue, and their plasma concentrations may roughly reflect activity of the disease.

Response to corticosteroid therapy is often excellent, but in rare cases, the administration of cyclophosphamide may be of value when corticosteroids do not prove efficacious. Still, progressive interstitial fibrosis may result and these patients, a small subgroup of cases with nonresponding disease, may eventually develop CRF [62, 69, 71, 74].

Analgesic Nephropathy

Analgesic nephropathy (AN) is a slowly progressive chronic renal disease characterized by renal papillary necrosis or calcifications and interstitial nephritis caused by excessive consumption of analgesic mixtures [75].

Since the discovery of an association between phenacetin use and the development of chronic interstitial nephritis, it has been recognized that drug-related renal disease is in large part a preventable disease. Discontinuation of heavy analgesic use may slow or stop progression of renal disease [76]. However, replacement of phenacetin with its major metabolite acetaminophen has not always been followed by a reduction in the incidence of analgesic nephropathy, suggesting that other drugs may play a role in this disease [77]. Several-case controlled studies and 2 prospective studies demonstrated the association between analgesic abuse and nephropathy [75]. However, the nephrotoxicity of the different analgesic products has not been clearly established [78]. The prevalence of analgesic nephropathy is related to the persistent daily consumption of widely available over-the-counter (OTC) mixtures containing 2 analgesic components plus caffeine and/or codeine [79]. This relationship could not be observed for analgesics containing only one analgesic component plus caffeine and/or codeine, although experimental data suggest nephrotoxicity of single analgesics [77, 78, 80]. The prevalence of analgesic nephropathy in patients with terminal kidney disease receiving dialysis varies widely between countries in Europe and outside Europe. In the early 1990s

the incidence was 0.8% in the US, 2% in Europe, and 9% in Australia [79]. In Scotland, Switzerland, Belgium, and Australia, it is a relatively common cause for chronic renal failure accounting for 10 – 20% of patients with ESRD. Recent analysis shows a changing pattern of prevalence and age distribution of analgesic nephropathy as a cause of ESRD. The EDTA registry reveals a declining incidence of analgesic nephropathy in the last decade in the age group under 64 years, while the incidence in the older age group remained high [81]. The same trends are observed in Australia [82]. These data indicate a real reduction in the incidence of analgesic nephropathy.

– *Pathology:* The pathologic abnormalities in analgesic nephropathy are nonspecific. The development from the earliest detectable lesions to end stage with bilateral shrinkage of the kidneys can be subdivided into the following 3 steps. The earliest detectable morphological lesion in patients with analgesic nephropathy is capillary sclerosis, which is found to be especially pronounced in the vessels of the renal pelvis and ureteral mucosa. The most pronounced capillary alterations are found in the proximal ureter. As a further morphological alteration, renal papillary necrosis follows. This lesion represents damage to the inner renal medulla that may be based on capillary sclerosis. Perhaps as a consequence of papillary necrosis, TIN may develop. Light microscopic investigations show a fibrotic interstitium with tubular atrophy and sporadic mononuclear cell infiltration. Sometimes concomitant focal glomerular sclerosis and interstitial calcifications can be found. At the time of clinical presentation, the kidneys are typically small [83 – 85].

– *Pathophysiology:* Experimental data show that the combination of acetylsalicylic acid with phenacetin or paracetamol induces severe medullary lesions more frequently than does either of these agents alone [77]. These results are in accordance with clinical and epidemiological observations in patients with analgesic nephropathy. The pathogenesis of analgesic nephropathy is related to the ability of the kidney to concentrate drugs in the papillae. For example, after ingestion of phenacetin and aspirin, phenacetin is converted in the gut and liver to acetaminophen by first-pass metabolism. Acetaminophen is normally metabolized in the liver and kidney by cytochrome P450 enzymes. After ingestion of large quantities, acetaminophen becomes concentrated in the papillae of the kidney during physiologic antidiuresis and undergoes oxidative metabolism by prostaglandin H synthase to biologically reactive intermediates. These are normally intercepted by reduced glutathione, which is present in excess within the renal cells. If acetaminophen is ingested alone, sufficient glutathione is generated in the papillae to detoxify the reactive intermediates [86, 87]. However, if acetaminophen is ingested with aspirin, the aspirin is converted to salicylate, which becomes highly concentrated in the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. The mechanism is not completely understood. However, the inhibition of NADPH production via the pentose shunt is a possible explanation. With the cellular glutathione depletion, the biologically reactive intermediates of acetaminophen then produce peroxides and arylation of tissue proteins, resulting in cellular dysfunction and necrosis of the

papillae [88, 89]. In addition, the inhibition of prostaglandin synthesis can exacerbate medullary damage from ischemia [90]. No evidence exists for the development of analgesic nephropathy with acetaminophen alone. Experimental data suggest that aspirin seems to be the most nephrotoxic of the commonly available analgesics and that combination therapy with aspirin is required for medullary damage in rats [91, 92].

– *Clinical Features*: The clinical course of analgesic nephropathy is frequently asymptomatic for years until the late stages of renal insufficiency. The earliest renal manifestation is caused by impaired tubular function. As a result of decreased urine concentrating ability, patients develop increased urinary frequency or urgency and nocturia. Additionally, an acquired form of RTA may contribute to the development of nephrocalcinosis. More than half of patients have pyuria, which, if persistently associated with sterile urine, provides an important clue to the diagnosis. Additionally, slight proteinuria may be present, whereas a protein excretion of more than 3g/24 hour may indicate a concomitant glomerular lesion. Macroscopic and microscopic hematuria may appear in the course of sloughing and elimination of fresh renal papillary necrosis, as a result of UTI, or, especially in the later stage, as a sign of uroepithelial carcinoma, which occurs with increased frequency in these patients. It is not known which analgesics predispose to carcinogenesis, seen after an average latency period of > 20 years [93, 94]. Therefore, even after termination of analgesic abuse, regular urine cytology and evaluation of the urinary tract should be undertaken for hematuria in these patients. Arterial hypertension is present in about 50% of patients with analgesic nephropathy. The hypertension seems to be renin dependent, because it may be exacerbated by volume depletion [95]. Additionally, acute papillary necrosis can evoke hypertensive crisis. Occasionally, shedding of papillary necroses into the efferent urinary tract may be associated with hematuria and even renal colic owing to obstruction of a ureter by necrotic tissue. Bacterial UTIs occur frequently and are late complications. With decreasing glomerular filtration rate (GFR), all metabolic signs of renal insufficiency may be present [95, 96].

  Besides the renal manifestations, a broad spectrum of extrarenal complications of chronic analgesic abuse can occur and often precedes the signs of analgesic nephropathy (Table 7). Women are affected 5 – 7 times more than men [95, 96].

– *Diagnosis:* Because there is no gold standard in the diagnosis of analgesic nephropathy, clues suggestive of the disease include a history of regular analgesic consumption, symptoms of an analgesic abuse syndrome, especially anemia, out of proportion to the degree of azotemia, renal colic without signs of nephrolithiasis, papillary necrosis, and sterile pyuria.

  CT scan without contrast medium is recommended to diagnose analgesic nephropathy in all patients with ESRD as well as those with mild and moderate renal insufficiency. The demonstration of bilateral decreased renal mass combined with either bumpy contours or papillary calcifications was found to have a high diagnostic value [97, 98].

– *Therapy:* There is no specific treatment for analgesic nephropathy. The primary goals of treatment are to prevent further

Table 7. Analgesic Abuse Syndrome

1. Nephropathy
   a) pathological findings
   – capillary sclerosis
   – papillary necrosis
   – tubulointerstitial nephritis
   b) clinical features
   – slowly progressive renal insufficiency
   – impaired tubular function
   – defect in urinary concentration
      – renal tubular acidosis
      – renal sodium loss
      – slight tubular proteinuria
   – hematuria
   – arterial hypertension
   – urethral obstruction
   – urinary tract infection

2. Uroepithelial carcinoma

3. Gastrointestinal complications
   – peptic ulcers and erosive gastritis
   – chronic pancreatitis

4. Hematological complications
   – anemia, out of the proportion to the degree of azotemia
   – mild hemolysis
   – methemoglobinemia (phenacetin)
   – agranulocytosis (pyrazolone derivates)
   – chronic hemorrhagic anemia (acetylsalicylic acids)

5. Skeletal complications, arthralgias

6. Typical skin color

7. Psychosomatic aspects
   – headache or chronic pain states
   – vegetative symptoms

renal damage. All suspect analgesics, particularly OTC medications, must be stopped to slow or stop progression of renal disease [76, 99].

The early treatment of complications, such as arterial hypertension, volume and sodium depletion, acute UTI, and urinary tract obstruction caused by renal papillary necrosis is important. Signs of kidney failure should be treated as appropriate for the extent and severity of the renal failure. Counseling, behavioral modification, or other interventions may assist in developing alternative methods for chronic pain control.

Patients undergoing renal transplantation as a result of analgesic nephropathy are at high risk of developing transitional cell carcinoma of the upper urinary tract. These tumors tend to be of high grade and stage, and affected patients have a poor outcome. Screening by urine analysis and voided urine cytology does not appear to be reliable for the early diagnosis of upper renal tract transitional cell carcinoma in the renal transplant patient. Therefore, annual cystoscopy and retrograde ureteric catheterization with washings, brushings, and radiological imaging should be performed to diagnose upper tract transitional cell carcinoma at an early stage. These patients should also be screened before transplantation using the same technique [100]. Considering the high mortality from urothelial carcinoma despite regular tumor screening in patients with analgesic nephropathy after renal transplantation, other investigators suggest that a bilateral nephroureterectomy should be performed prophylactically in patients with proven analgesic nephropathy [101].

Multiple Myeloma

Multiple myeloma is a malignant proliferation of plasma cells characterized by excessive production of monoclonal immunoglobulins (IgG ≈ 53%, IgA ≈ 25%, or IgD ≈ 1%) or light chains (Bence-Jones proteins) (≈ 20%). Renal dysfunction occurs in > 50%

of patients and can precede the nonrenal manifestations. The clinical presentation is characterized by renal failure, which is a major cause of death. The kidneys of patients with multiple myeloma can be damaged by multiple mechanisms (Table 8) [102].

Table 8. Factors Contributing to Nephropathy in Patients with Multiple Myeloma

– Excretion of light chains which may cause the following renal diseases:
Myeloma kidney
Light chain nephropathy
AL-Amyloidosis
– Hypercalcemia
– Hyperuricemia
– Dehydration
– Recurrent infectious pyelonephritis
– Renal plasma cell infiltration
– Contrast media or nephrotoxic agents

The myeloma kidney or cast nephropathy is the most common lesion resulting from light chain toxicity. It is characterized by large proteinaceous intratubular casts surrounded by multinucleated giant cells, probably of monocyte-macrophage origin [103]. The casts typically consist of Tamm-Horsfall protein and light chains [104]. As a consequence of cast formation, intratubular obstruction may develop. The tubules are extensively damaged and show tubular atrophy and fibrosis [105]. Additionally, plasma cell and mononuclear cell infiltration of the kidney, nephrocalcinosis, and amyloid deposits in the vessels and glomeruli may also be present. Light chain deposits can typically be observed by means of immunofluorescence staining in renal basement membranes (tubular, glomerular, and vascular) [106]. In addition, there is often concomitant deposition in the glomerular mesangium.

The pathogenetic causes of cast nephropathy are still unknown. When Bence-Jones proteins of patients with multiple myeloma or AL amyloidosis are injected into mice, the animals reproduce renal lesions identical to those observed in patients [107]. Myeloma casts develop in the distal nephron when cast-forming light chains bind to a specific portion of Tamm-Horsfall protein, secreted by cells of the thick ascending limb of the loop of Henle, to form an insoluble protein complex. Light chains are normally synthesized by plasma cells in excess of heavy chains. Because of their low molecular weight (approximately 22 kD), light chains are filtered at the glomerulus, reabsorbed by the proximal tubule, probably by receptor-mediated endocytosis, and catabolized [102, 108]. However, in the course of multiple myeloma and other diseases, light chain production is dramatically increased. With the increase in amount of light chains presented to the tubules, the proximal tubular reabsorptive capacity is overwhelmed, which leads to the urinary excretion of light chains as Bence-Jones proteins. The tubular damage results either directly from nephrotoxic effects of Bence-Jones proteins or indirectly from intrarenal obstruction from cast formation [105]. Interestingly, there are unexplained individual variations in the toxicity of Bence-Jones proteins [109, 110]. Some patients who excrete large amounts of light chains develop no renal dysfunction. Others show a nephropathy despite small urinary amounts of light chains.

A variety of factors modify the interactions between the light chains and Tamm-Horsfall protein and thus influence the development of renal failure [102, 111]. The coaggregation depends on the ionic environment and physicochemical factors, such as light chain concentration [112], isoelectric point [113], acidic intraluminal pH of the distal nephron [114], tubular flow rate [112], and presence of complete Tamm-Horsfall protein [115]. In-

Table 9. Factors Affecting Cast Formation [102]

– Concentration and type of Bence-Jones protein
– Concentration and carbohydrate content of Tamm-Horsfall protein
– Distal nephron milieu:
Sodium chloride concentration
Calcium concentration
Tubule fluid flow rate
Tubule fluid pH
Furosemide or radiocontrast agents

Table 10. Renal Manifestation of Multiple Myeloma

– Bence-Jones proteinuria, glomerular proteinuria
– Acute or chronic renal insufficiency
– Tubular dysfunction
Fanconi syndrome
Renal tubular acidosis
Defect in urinary concentration

creasing concentrations of sodium or calcium but not magnesium facilitate coaggregation [115]. Patients who excrete large amounts of Bence-Jones proteins in the urine are the most prone to renal failure. Some investigations suggest that cast-forming Bence-Jones proteins have isoelectric points > 5.1. This may explain the observation that aciduria independent of urinary flow rate increases the nephrotoxicity of Bence-Jones proteins [114] and that an acidic intraluminal pH of distal nephron may give an optimal environment for the precipitation [102]. Conditions in which the intraluminal flow rate are reduced, such as volume depletion, can accelerate tubular obstruction. Furosemide augments coaggregation and accelerates intraluminal obstruction in rats, possibly by increasing the intratubular sodium and calcium concentration [112].

Experimental data suggest that ionic interaction between Bence-Jones proteins and a specific peptide binding site on Tamm-Horsfall protein promotes heterotypic coaggregation [116]. However, the carbohydrate moiety of Tamm-Horsfall protein is also essential for coaggregation, perhaps by facilitating homotypic aggregation [116]. Deglycosylated Tamm-Horsfall protein does not coaggregate with Bence-Jones proteins and colchicine, which seems to remove the carbohydrate component of Tamm-Horsfall protein, thus prevents coaggregation of Tamm-Horsfall protein and toxic light chains in rats [112].

Table 9 summarizes the factors affecting cast formation.

– *Clinical Features:* Renal failure occurs in nearly 25% of patients, whereas renal dysfunctions occur in > 50% of patients. Recurrent bacterial infections, especially pyelonephritis, are presenting features in about 25% of cases. The clinical presentation of renal involvement in multiple myeloma is characterized by acute or chronic progressive renal insufficiency. However, according to the multifactorial pathogenesis of the renal dysfunction, clinical features are variable (Table 10). Proteinuria is found in 70% of all patients with multiple myeloma and may often be the initial symptom. It reflects overflow of monoclonal Bence-Jones proteins. Generally, there is very little albumin in the urine because glomerular function is usually normal. When the glomeruli are involved, the proteinuria is nonselective. The presence of a nephrotic syndrome and a monoclonal kappa or lambda light chain in the urine almost always indicates primary amyloidosis or light-chain depo-

sition disease, and a newly diagnosed albuminuria in patients with multiple myeloma is suspicious of AL amyloidosis. In addition, > 70% of patients show signs of tubular defects, such as impaired acidification or adult Fanconi syndrome, which is characterized by excessive increased urinary loss of glucose, phosphate, and all glomerular filtrated amino acids. In addition, loss of bicarbonate induces RTA (type 2 proximal RTA), and the urinary concentrating ability may also be diminished [109, 117 – 120].

– *Diagnosis:* The diagnosis of multiple myeloma should always be considered when a patient > 50 years of age develops renal failure and proteinuria of unknown origin. The classic triad of multiple myeloma is a bone marrow specimen containing > 10% atypical or immature plasma cells, lytic bone lesions, and a serum and/or urine M component. Additionally, multiple myeloma should be considered when renal insufficiency is accompanied by hypercalcemia, inadequate anemia, and/or elevated erythrocyte sedimentation rate (ESR). Characteristically, dipsticks for detecting proteinuria are not reliable at identifying light chains. However other qualitative techniques that depend on precipitation of protein, such as the sulfosalicylic acid (SSA) method, are useful in detecting Bence-Jones proteinuria. Thus, the constellation of a negative dipstick test and a positive precipitation test can be due to the presence of Bence-Jones proteins. This should be further evaluated by electrophoresis and immunoelectrophoresis. Typically, a decreased anion gap can be found in patients with multiple myeloma because the M component is cationic, resulting in retention of chloride. The kidneys are normal size on ultrasound.

Table 11. Potential Therapies for Cast Nephropathy [102]

– **Chemotherapy to decrease Bence-Jones protein**
– Plasma exchange to remove light chains from plasma
– Increase free water intake to 2–3 L/day as tolerated
– Treat hypercalcemia
– Avoid exposure to furosemide and radiocontrast agents
– Alkalinize urine
– Colchicine to decrease amount and carbohydrate content of Tamm-Horsfall protein
– Reducing agents that alter the light chain binding site on Tamm-Horsfall protein

– *Therapy:* Treatment strategies for myeloma kidney (Table 11) are somewhat controversial. The principle of therapy has been chemotherapy to decrease production of the abnormal monoclonal immunoglobulins and immunoglobulin light chains. Clinical data indicate that plasma exchange associated with chemotherapy rapidly removes large amounts of light chains and improves both renal function and long-term survival expectancies of patients suffering from ARF due to multiple myeloma with Bence-Jones proteinuria [121, 122]. Little attention has been given to understanding and disrupting the pathophysiologic mechanisms involved in production of intraluminal casts. Noncontroversial elements include the supportive treatment of hypercalcemia (corticosteroids, hydration, 0.9% sodium chloride infusion, calcitonin, bisphosphonates) and hyperuricemia (allopurinol, hydration, urinary alkalinization). Adequate hydration is necessary (daily intake of 2 – 3 L of fluids as long

as there are no signs of renal failure or heart insufficiency) to keep the urine flow high. Additionally, the sodium chloride concentration in the distal nephron should be lowered. Experimental data in rats show that urinary alkalinization prevents renal failure from Bence-Jones proteins. However, comparable results in human patients are missing. Radiocontrast media and nephrotoxic agents should be avoided. Furosemide can increase distal tubular sodium chloride and calcium concentrations and can enhance, in a concentration-dependent fashion, toxicity of cast-forming proteins in vivo. Particularly in the setting of volume depletion, loop diuretics should be used with caution because of their capability to augment coaggregation of light chains with Tamm-Horsfall proteins. Experimental data in rats suggest that treatment with colchicine prevents aggregation of cast-forming Bence-Jones proteins, apparently by decreasing the excretion and removing the carbohydrate moiety of Tamm-Horsfall protein [112]. Colchicine, in daily doses of 1 – 2 mg, is standard therapy in preventing renal amyloidosis from familial Mediterranean fever. Colchicine in this dosage might also be efficacious in managing patients with cast nephropathy. Additionally, reducing agents such as cysteamine (beta-mercaptoethylamine) alter the tertiary structure of Tamm-Horsfall protein sufficiently to diminish subsequent binding to light chains. However, the possible role of colchicine and reducing agents in the management of myeloma kidney requires further clinical studies [102].

Kidney transplantation has been performed in a small number of patients with myeloma kidney. Although recurrence of cast nephropathy has been described, the results support the strategy of offering cadaver renal transplantation to carefully selected individuals who require long-term dialysis and whose myeloma is in remission after chemotherapy [123 – 125].

Uric Acid

Hyperuricemia can cause different renal disorders (Table 12). The term gouty nephropathy is used for the chronic interstitial nephritis with hyperuricemia and gouty arthropathy. While it is commonly accepted that hyperuricemia can cause ARF this has not been unequivocally established for chronic interstitial disease [126]. Experimental data support the hypothesis that interstitial deposits of urate and uric acid in the kidney may be derived from intratubular deposits that react with the tubular epithelium and pass into the interstitium. Loss of tubular integrity may not be a prerequisite for crystal migration [127]. However, there are no convincing data to verify an association between an overproduction of uric acid and progressive renal failure. Moreover, it has been reported that lead intoxication may be the pathogenically relevant agent in gouty nephropathy [128]. However, many patients with impaired renal function present with high serum uric levels secondary to diminished GFR and tubular effects of diuretic drugs. Lowering of uric acid production could be important in these patients if hyperuricemia leads to acceleration of renal dis-

Table 12. Hyperuricemia-associated Renal Disorders

Nephrolithiasis
Acute renal failure in excessive overproduction
Gouty nephropathy

ease. Besides encouraging water intake (urinary volume > 2 L/day), a restriction of alimentary purine, alkalization of urine, and allopurinol in doses adjusted to renal excretory function should be considered in patients with serum uric acid > 10 mg/dL (600 μM) [127].

Heavy Metal Intoxication

Chronic lead and cadmium exposure injure the proximal tubular cells initially. Hence, tubular transportation defects may be detected. However, as stated above, these findings are not specific in tubulointerstitial diseases. The pathogenetic mechanisms by which tubular lesions in heavy metal nephropathies result in chronic tubulointerstitial inflammation and fibrosis remain to be elucidated. Expression of pro-inflammatory mediators by injured epithelial cells may lead to mononuclear cell infiltration and activation of cytotoxic T lymphocytes. CTIN in chronic lead and cadmium intoxication will be discussed in more detail. In addition, intoxication with several other metals such as mercury, thallium, chromium, lithium, and nickel may lead to CTIN [129].

– *Lead Nephropathy:* Chronic exposure to lead can be associated with CRF displaying the pathological features of CTIN (see also above) [130]. Lead ingestion can arise from occupational exposure as well as from household sources (e.g. pottery, crystal, old water pipes). Lead accumulates in the S_3 portion of the proximal tubular cells, leading to dysfunction ranging up to full expression of the Fanconi syndrome [131]. Proximal tubular lesions are usually accompanied by additional chronic interstitial nephritis with interstitial fibrosis, atrophy, and nephrosclerosis [132]. Clinical signs of lead nephropathy are hyperuricemia and hypertension. Recurrent gout in the presence of CRF is a useful marker of chronic lead poisoning [133]. The diagnosis of lead nephropathy is based on an augmented urinary lead excretion (>0.6 mg/24hours) following EDTA administration (2 doses of 1 g), while blood lead levels are less useful to determine a chronic exposure [134]. EDTA chelation therapy is suggested thereafter until lead mobilization becomes normal again, with a favorable outcome in some cases. In contrast to the course in adults, lead exposure in children only rarely results in CRF [134].
– *Cadmium Nephropathy:* Occupational and less often environmental (itai-itai disease) [135, 136] excess cadmium exposure result in tubular injury and interstitial nephritis. Metallothionin-bound cadmium is pinocytosed into proximal tubular cells leading to proximal tubular dysfunction and especially to hypercalciuria. A high incidence of metabolic bone disease and complications due to nephrolithiasis are special features of this entity, often being the initial symptoms. The diagnosis can be confirmed by the finding of a high urinary excretion of cadmium. Besides symptomatic treatment of bone disease and complications, there are to date no specific therapeutic options in cadmium nephropathy. Large amounts of cadmium are stored within the liver and kidneys, and the half-life ($t^{1/2}$) is > 10 years .

Hypercalcemia

The kidneys can be affected in many ways by hypercalcemia. Elevated serum calcium levels and excessive hypercalciuria in diseases with high calcium turnover often lead to an acute deterioration of renal function. Increased cholecalciferol in sarcoidosis or in

patients with excessive vitamin D intake are less frequent causes than paraneoplastic calcium release due to parathormone-related peptide or bone metastases. Tubular transportation disorders with ensuing hypercalciuria are rare. In hypercalcemia, it is believed that direct vasocontractory effects, a reduction in glomerular filtration coefficient, and volume depletion due to a vasopressin-resistant concentrating defect result in a decline of GFR [137, 138]. Apart from acute effects on renal function, hypercalcemia may also lead to a deposition of calcium within the tubulointerstitium (especially medullary tubular basement membrane, collecting ducts, and finally throughout the interstitium), so-called nephrocalcinosis [63, 139]. These tubulointerstitial calcium lesions in turn lead to inflammatory infiltration and chronic tubulointerstitial disease. Nephrocalcinosis can be diagnosed either by ultrasonography or by computed tomography (CT) as well as by plain X-ray imaging techniques. Diagnosis of the underlying disease is essential to enable specific treatment. Treatment and nonrenal complications of hypercalcemia itself are discussed in chapter I.5. In general, the outcome of acute deterioration of renal function is good if treated early depending on the cause of the hypercalcemia. In nephrocalcinosis, treatment results are less favorable than with all other forms of chronic tubulointerstitial disease.

Hypokalemia

Chronic hypokalemia is another albeit rare electrolyte disorder that can cause tubulointerstitial nephritis. Inherited forms of hypokalemia are primary renal tubular transportation defects that lead to wasting of potassium into the tubular lumen (often accompanied by acid-base disorders and other defects). These forms of CTIN usually show slow progression towards ESRD. Hypokalemia nephropathy is characterized morphologically by vacuolization of proximal tubular cells, the origin of which is unknown. In addition to the histologic findings of chronic tubulointerstitial nephritis and fibrosis, periodic acid-Schiff (PAS)-positive intracytoplasmic granules and cyst formations within the renal medulla can be observed. Functionally, hypokalemia can lead to marked polyuria that is resistant to antidiuretic hormone (ADH). Experimental data in rats reveal that excessive synthesis of ammonia may initiate an inflammatory response, with tubulointerstitial damage caused by concurrent complement activation [140]. Potassium repletion is essential and can reverse both functional and structural abnormalities in many cases.

Oxalosis

Hyperoxaluria can be caused by at least 2 hereditary disorders of oxalate metabolism: excessive oxalate load or an increase in bowel absorption of oxalate. Though relatively rare, inborn oxalate disorders often result in chronic renal disease and early end-stage insufficiency. Primary hyperoxaluria (PH) type 1 is characterized by the deficiency of the liver enzyme alanine glyoxylate aminotransferase, and the very rare PH type 2 is based on a defect of the D-glycerate dehydrogenase [141, 142]. Patients with lesions of large portions of the small bowel, especially the terminal ileum in inflammatory bowel disease, or with short bowel syndrome after surgery may have increased absorption of oxalate. An increased bile acid load in the large bowel is believed to capture calcium from calcium-oxalate complexes, thereby releasing free oxalate for absorption. In addition, ethylene glycol poisoning or ascorbic acid overdoses can result in excessive metabolic oxalate production and tubulointerstitial damage. Deposition of cal-

cium-oxalate crystals in many tissues and organs is the pathogenically relevant lesion. Besides renal involvement, deposition in the bones, in arteries, and in nervous tissue results in severe lesions that lead to a clinically prominent bone disease with fractures, ischemic damage, and polyneuritis as well as retinal lesions. In the kidney, nephrolithiasis, obstruction of the tubular lumina, and interstitial deposition of crystals are the main manifestations. Measures to lower oxalate often are ineffective to prevent CRF (and extrarenal damage). The most effective prophylactic treatment is increasing urinary output by augmenting water intake to 3 – 4 L/m^2/day. Administration of citrate, orthophosphate, or magnesium can prevent crystal formation and should be given additionally. Some cases of PH type 1 also respond to pyridoxine (a cofactor of enzyme activity). Patients with ESRD due to PH type 1 are reported to benefit from combined liver-kidney transplantation with good results in a number of cases associated with improvement of extrarenal manifestations [143, 144].

Radiation Nephritis

Radiation nephritis has become rare during recent years because administration protocols for radiation were changed to lower the total dose on the kidneys when nearby target organs are to be treated. However, total body irradiation in patients receiving bone marrow transplantation is an increasing cause of radiation damage of the kidneys. Radiation nephritis is clinically divided into acute forms with a clinical onset within one year and more delayed reactions to radiation after several years.

Acute forms present with hypertension and chronic anemia as well as edema. In most cases, a progressive renal insufficiency will result in ESRD. Occasionally, varying degrees of proteinuria and microscopic hematuria are found. Especially in children, acute radiation nephritis may be associated with intravascular hemolysis, making differentiation from the hemolytic uremic syndrome (HUS) difficult.

In chronic forms, patients may present with often isolated hypertension or mild proteinuria even after more than a decade. Malignant hypertension can occur, probably due to lesions of the renal arteries, at least in some cases. Severe forms of CRF with hypertension and proteinuria can also be seen.

Histologic lesions of chronic tubulointerstitial fibrosis are found in radiation nephritis. Acute forms display signs of marked glomerular endothelial lesions as well. Inflammatory infiltrates are usually absent, probably secondary to the therapy and primary disease. The pathogenesis of radiation injury of the kidneys is believed to be primarily vascular with endothelial cell damage resulting in progressive vascular disease with ensuing tubular atrophy and generalized ischemic lesions of the tubulointerstitium. In addition, the tubular epithelium is affected primarily by irradiation. Recent data on fibroblast cell regulation suggest that parenchymal cells and especially fibroblasts may be in part responsible for fibrogenesis after radiation [145, 146]. As with other forms of progressive renal disease, administration of ACE inhibitors could prove advantageous [147]. Hypertension due to unilateral disease may respond to nephrectomy of the affected kidney. Radiotherapy involving the kidneys exacerbates the risk for renal toxic injury by nephrotoxic drugs (radiocontrast agents, antibiotics, and especially cytotoxic drugs). Hence, careful management of radiation along with additional therapy is necessary.

Course and Treatment

In most forms of CTIN, the primary disease cannot be treated sufficiently (specific therapies of some special entities have been discussed before). Moreover, even if further renal injury can be prevented, renal function slowly but inevitably deteriorates towards CRF, once a certain degree of tubulointerstitial damage and especially fibrotic changes have occurred (in cases of CTIN as well as in essentially all chronic renal disorders). The most important maneuver is controlling blood pressure (lowest tolerable blood pressure ≤ 140/85 mmHg) preferably with ACE inhibitors unless otherwise contraindicated [148]. These drugs seem to possess a higher nephroprotective potency than other antihypertensive substances Angiotensin II type I receptor antagonists may prove comparably effective in the future [149]. To date, however, evidence for the nephroprotective properties of ACE inhibitors is only documented in type-I diabetes mellitus [150]. Thus, treating elevated blood pressure, irrespective of the individual antihypertensive agents, remains the main goal. In addition, treatment of accompanying abnormalities such as hyperuricemia, metabolic acidosis, and hyperphosphatemia is advisable. The impact of a low protein diet on the progression of CRF is not clear [151 – 153]. We advise our patients to restrict protein intake to 0.8 g/kg/day (plus urinary losses). However, great care must be taken to prevent a catabolic state in these patients.

Vascular Diseases of the Kidney

A large variety of renal diseases are of vascular origin. They may be classified as lesions affecting the large blood vessels (renal artery and vein) or primarily the small vessels and capillaries of renal parenchyma. The latter disorders and subtotal renal artery stenosis associated with hypertension are discussed elsewhere in chapter I.21. Thus, this chapter will focus on diseases of the large vessels only, namely renal artery thrombosis and embolism, cholesterol embolism syndrome, and renal vein thrombosis. These entities are similar in that they are usually associated with acute failure of the affected kidney. Hence, depending on pre-existing renal function and the extent of the lesion (unilateral or bilateral), they may cause acute azotemia. Table 13 summarizes renal vascular diseases.

Renal Artery Thromboembolism

The term renal artery thromboembolism implies thromboembolic phenomena to the main renal arteries and the development of thrombosis in the renal artery.

The source of thromboembolic phenomena is usually the left atrium in patients with atrial fibrillation or the left ventricle with wall-adherent thrombi, shortly after myocardial infarction [154 – 156]. Less often, embolism might arise from endocarditis-associated thrombotic lesions (bacterial or aseptic). Additionally, rheumatic valvular disease and prosthetic heart valves are predisposing factors [155, 156]. Incidences with paradoxical embolism from venous thrombi through asso-

Table 13. Renal Vascular Diseases

Diseases of the renal artery and branches
Renal artery thrombosis
- – Renal vascular hypertension / ischemic disease
- – Atheromatous
- – Fibromuscular dysplasia

Renal artery embolism
- – Atrial or ventricular embolism
- – Aortal origin
- – Septic embolism (endocarditis)
- – Lupus anticoagulant syndrome

Dissection (aortal)
Cholesterol embolism syndrome
Large vessel vasculitis
- – Takayasu
- – Polyarteritis nodosa

Diseases of the small renal vessels
Small vessel vasculitis
- – Wegener granulomatosis
- – Microscopic polyangiitis
- – Henoch-Schönlein purpura

Renal allograft rejection
Radiation nephritis (see CTIN)
Lupus anticoagulant syndrome
Disseminated intravascular coagulation
Toxemia of pregnancy
Hemolytic uremic syndrome / thrombotic-thrombocytopenic purpura

Diseases of the renal vein
Renal vein thrombosis
- – Nephrotic syndrome
- – Heparin-induced thrombopenia type II
- – Hyperviscosity syndromes (e.g. Polycythemia vera, Leukemias, Thrombocytosis)
- – Diseases of the clotting system (inherited, lupus anticoagulant syndrome, etc.)
- – Infiltration by tumor (e. g. renal cell carcinoma)

Compression of the renal vein
- – Lymphoma
- – Pancreatic carcinoma

Oral contraceptives

ciated right to left shunting are very rare [157]. Diseases such as tumors and aneurysms may result in embolism and must be considered [158, 159]. Percutaneous intraarterial catheterization and aortography can cause an embolism involving the renal artery and aorta [160]. Renal artery embolism is bilateral in up to one-third of cases.

Renal artery thrombosis (RAT) is much less common than renal artery occlusion by emboli [161]. The latter is usually superimposed on an atheromatous plaque (as in coronary thrombosis). In addition, intimal lesions of the renal artery arising from trauma or surgery as well as inflammatory injury can cause thrombotic occlusion [162]. Numerous other factors have been associated with RAT. For example, ACE inhibitors may induce RAT in patients with renal artery stenosis [163 – 165]. RAT can also be associated with erythrocytosis, factor V Leiden mutation, antiphospholipid syndrome, or elevated cyclosporine levels [166 – 169]. Spontaneous renal artery thrombosis is a rare phenomenon [161].

Clinical and Laboratory Features

Initially, patients usually complain of a sudden onset of flank pain, abdominal or chest pain, nausea, and vomiting. Fever and chills may occur. The physical examination often reveals abdominal or flank tenderness, sometimes accompanied by clinical signs of peritoneal irritation. The extremities and central nervous system (CNS) should be carefully evaluated for signs of embolization. Considering the nonspecific symptoms, an early diagnosis of renal arterial thromboembolism is often difficult [170, 171].

Laboratory findings include leukocytosis, proteinuria, hematuria, and elevated levels of lactic dehydrogenase (LDH), serum glutamic-oxalacetic transaminase (SGOT), se-

rum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, and creatinine kinase (CK) [170, 172, 173]. CK isoenzyme assay for CK-MB may be falsely high, due to a release of CK-BB activity from renal tissue. Deterioration of renal blood flow results in acute oliguric failure of the affected kidney, which can be compensated from a functioning contralateral organ. Anuria suggests the presence of bilateral emboli. Another result of renal ischemia is renin release leading to arterial hypertension [174]. If the onset is rather slow and occlusion is subtotal, only hypertension may result.

Various techniques can be employed to establish the diagnosis. Dopplerultrasonography, perfusion scintigraphy, and CT scan as well as magnetic resonance imaging (MRI) with contrast agents are highly sensitive and specific techniques [175 – 179]. Intraarterial angiography is the definitive method for the diagnosis of renal artery thromboembolism [159]. However, this technique should be used only when a therapeutic intervention is planned because of the risk of ARF induced by contrast media.

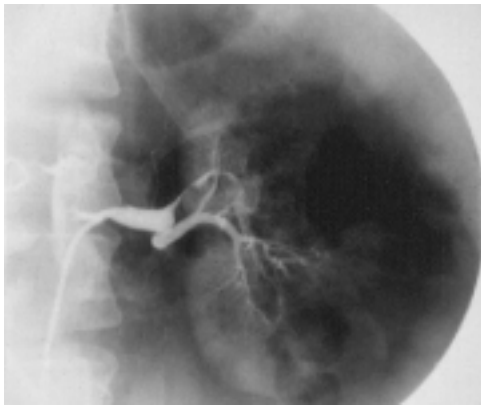

Figure 7a. Preinterventional intraarterial angiography of a 48-year-old-man with patent foramen ovale who had an embolism to the anterior main branch of the left renal artery. Consequently, renal perfusion was dramatically diminished.

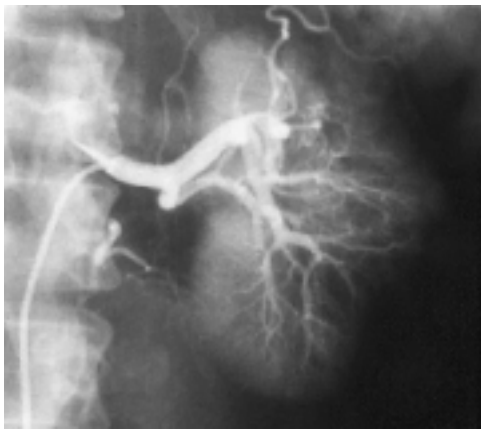

Figure 7b. Intraarterial angiography after successful intraarterial thrombolysis (urokinase) shows recanalization of the affected arterial branch and restoration of renal blood flow.

Therapy

Intraarterial angiography allows immediate therapy in many cases. This will mean percutaneous transluminal angioplasty (PTA) and embolectomy with or without stenting of the vessel wall [180 – 182]. In some instances, vascular surgery will be needed. However, traditional methods of repair (e.g. in situ repair, bypass graft, and thrombectomy) have poor success rates. Renal autotransplantation was successfully performed in a patient with bilateral RAT [183]. If none of these therapeutic options can be employed, intraarterial or systemic thrombolysis (e.g. streptokinase or urokinase) should be considered to prevent irreversible loss of the organ [154, 184, 185] (Figures 7a and 7b). In any event, therapy should be started as soon as possible [186]. However, even after a one day delay, renal function in some patients will still profit from therapy because renal parenchyma may be perfused via collateral vessels or by minimal flow rates through the affected vessel [187, 188]. Conservative treatment by anticoagula-

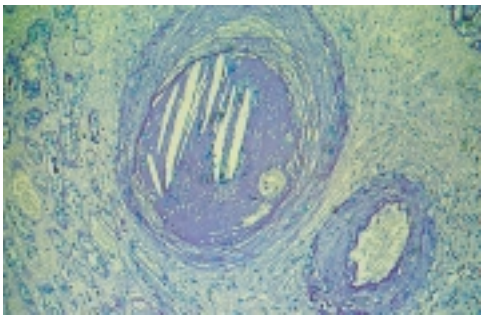

Figure 8. Renal cholesterol atheroembolism of an interlobular artery in a kidney transplant of a 70-year-old male. A fibrinous thrombus, containing typical cleft-like spaces of cholesterol crystals, is obstructing the lumen. Note edema and the ischemic tubular lesions in the surrounding interstitium (PAS, magnification x 125).

tion with heparin and acetylsalicylate is usually not sufficiently effective. However, long-term anticoagulation may be required in some patients to prevent embolization to other vital organs.

Cholesterol Crystal Embolism

Cholesterol crystal embolism syndrome (CCE) occurs mainly in elderly patients (>60 years) frequently with a history of hypertension, atherosclerotic cardiovascular disease, renal failure, and aortic aneurysms (25%) at presentation (Figure 8). To a lesser extent, patients with thrombolytic or anticoagulant therapy are also affected. Possible predisposing factors are operative, radiological, and vascular procedures. Finally, there are reports that cholesterol embolism can occur spontaneously. Multiple showers of cholesterol emboli that stem from atheromatous plaques may lodge in medium-sized vessels (diameter < 200 μm). Here they initiate a progressive inflammatory reaction. Initially, an infiltrate of macrophages and giant cells is found. This is followed by a process of intimal proliferation and fibrosis and results in irreversible occlusion of the arteries [189 – 191].

Clinical and Laboratory Features

CCE frequently presents with nonspecific manifestations that mimic other systemic diseases. The onset can be abrupt, but more chronic courses of progressive loss of organ functions can also be found. Clinical manifestations vary, depending on the affected organs, up to multiorgan failure. The brain, retinal arteries, and visceral vessels (pancreas, gut) are often involved. Also, embolism of muscles and skin is usually found. Thus, ischemic necrosis of the toes (blue toe syndrome) and livedo reticularis may occur and may be mistaken for vasculitis. In the kidneys, embolism results in deterioration of renal function and a mixture of mild proteinuria, microscopic hematuria, and leukocyturia. Additionally, nonspecific signs and symptoms such as fever, weight loss, myalgias, and headache may appear. Only one-third of CCE cases are diagnosed premortem, most commonly by biopsy of the muscle, skin, and kidney. Mortality is high and is most commonly due to multifactorial, cardiac, and renal etiologies. CCE should always be considered in elderly patients with atherosclerotic vascular disease with onset of renal insufficiency and cutaneous manifestations. In addition, thorough inspection of the retinal arteries may reveal cholesterol emboli. The emboli may be seen as bright copper yellow plaques, usually lodged at the bifurcations of retinal arterioles. In many cases however, the diagnosis will be missed unless renal biopsy demonstrates the presence of cholesterol emboli within the smaller arteries [190 – 192].

Laboratory findings are indistinct, but eosinophilia and increased ESR are often present.

Diagnosis of this disorder is difficult, as findings in urinalysis are rather nonspecific. Eosinophilia may be suggestive in combination with a history of predisposing procedures and skin findings [190 – 192].

Therapy and Prognosis

To date, there is no specific treatment available, and CRF (as well as marked impairment from other manifestations) can often develop. Treatment of arterial hypertension may slow progression of renal insufficiency. ACE inhibitors may be beneficial to control arterial hypertension. Cholesterol-lowering agents are used as well [193]. They may stabilize the vascular plaque and therefore prevent further embolization. Prostacycline analogs are novel candidates for the treatment of cholesterol embolism [194]. The role of anticoagulation is controversial. It may predispose patients to the development of CCE [195]. Case reports of catastrophic cholesterol embolization temporally associated with thrombolytic therapy patients have suggested a causal relationship. The prevalence of cholesterol embolization in patients with acute myocardial infarction treated with thrombolytic therapy is not significantly higher than in those treated without thrombolytic therapy. Isolated case reports of severe cholesterol embolization temporally associated with thrombolytic therapy do not represent a phenomenon with widespread subclinical occurrence [196].

Renal Vein Thrombosis

Thrombosis or occlusion of one or both renal veins occurs in a variety of settings (Table 14).

Table 14. Causes of Renal Vein Thrombosis

– Extrinsic compression (tumor, lymph nodes, aneurysm, retroperitoneal mass)
– Invasion of the renal veins or inferior vena cava by renal cell carcinoma
– Trauma
– Hemoconcentration (children in association with dehydration)
– Nephrotic syndrome
– Kidney transplantation (OKT3 and cyclosporine therapy)
– Steroid administration
– Pregnancy or oral contraceptives
– Constitutional protein S deficiency [197]
– Acute pyelonephritis [198]
– Primary antiphospholipid syndrome [199, 200]

The association between renal vein thrombosis (RVT) and nephrotic syndrome was first described by the French nephrologist Rayer in 1840 [201]. In the past, most cases of RVT were diagnosed postmortem. Later, with the development of more advanced imaging techniques and selective catheterization, antemortem diagnosis of RVT was made possible and the number of described cases increased. So far, however, there is controversy about the real incidence of RVT in adults with the nephrotic syndrome. The incidence of RVT in the adult population is difficult to establish, because RVT frequently occurs without a specific clinical presentation, and therefore the diagnosis is often missed.

Thromboembolism is one of the most serious complications of the nephrotic syndrome [202, 203]. The most frequent site of thrombosis is the renal vein, with a reported incidence varying from 2 – 42% (average incidence 9%) [204]. The prevalence of RVT in patients with all types of nephrotic syndrome other than membranous nephropathy (MN) who were submitted to venography was 13% [204]. On the other hand, the mean frequency of RVT in patients with the nephrotic syndrome caused by MN was 15.4% (5 – 62%)

and increased to 29.6% when renal venograms were performed [204]. It is generally accepted that MN is the most common nephropathy associated with RVT. Other forms of nephropathy such as membranoproliferative glomerulonephritis (MPGN), lupus nephritis, and amyloidosis are not frequently associated with RVT [205]. For poorly understood reasons, nephrotic syndrome due to diabetes mellitus, focal sclerosis, and minimal change disease does not carry a high risk of RVT. It remains unexplained why there is a selective association between MN and RVT that does not completely exclude a possible pathogenetic correlation between primary RVT and the subsequent MN in selective patients [204]. It seems that the disease process underlying the nephrotic syndrome may play a paramount role in the genesis of RVT or thromboembolic phenomena [205]. In addition, RVT is very frequently complicated by pulmonary emboli. Approximately 42% of all patients with the nephrotic syndrome have thromboembolic complications that were more frequent in MN compared with other types of the nephrotic syndrome [204].

RVT is thought to be a result of the profound metabolic disorder due to the nephrotic syndrome. Alterations of many coagulation factors and clotting inhibitors as well as defects in the fibrinolytic system and platelets may arise. Table 15 summarizes the major factors that may contribute to the hypercoagulable state in the nephrotic syndrome [203, 204, 206].

In summary, the hypercoagulable state of the nephrotic syndrome seems to be characterized by occasionally low zymogen factors, a marked increase in cofactors, an increase in plasma fibrinogen, sometimes a decrease in antithrombin III, and an increase in α 2-antiplasmin. Additionally, thrombocytosis and increased platelet aggregation are observed. However, none of the various laboratory tests used so far can predict the development of thrombotic complications [207]. Additionally, hypoalbuminemia also might play a role in the platelet hyperaggregability in the nephrotic syndrome because albumin normally binds arachidonic acid, thus limiting its conversion to thromboxane A2 by platelets. Hypoalbuminemia might cause increased platelet archidonic acid metabolism, and therefore platelet hyperactivity may result [208]. As a consequence of these abnormalities in blood coagulation, a hypercoagulable state may develop. In addition, further clinical events or individual predisposition such as increased blood viscosity, intravascular volume deple-

Table 15. Major Factors Contributing to the Hypercoagulable State in the Nephrotic Syndrome

Coagulation factor	Abnormality
Zymogens	Factor XII ↓ Factor XI ↓↑ Factor IX ↓↑ Factor VII ↓↑
Cofactors	Factor V ↑ Factor VIII ↑
Fibrinogen	↑
Fibrinolytic system	Plasminogen ↓ Plasminogen activator ↓
Regulatory proteins	Antithrombin III ↓ alpha 2-antiplasmin ↑ alpha 2-macroglobulin ↑ alpha 1-antitrypsin ↓ protein C ↑ protein S ↑
Platelets	Count ↑ Adhesiveness ↑ Aggregation ↑
Endothel	Altered endothelial-cell function

tion, or other therapeutic maneuvers (e.g. steroid therapy, diuretics) may trigger the disease.

Clinical Features

Only 10% of patients with RVT present with clinical symptoms [203]. Acute RVT should be considered whenever an acute change in renal function or increase in proteinuria is noted in a setting of nephrotic syndrome. A sudden onset of persistent flank pain, which may be colicky at times, marked costovertebral angle tenderness, macroscopic hematuria, changes in urinary protein excretion, and increased renal size are features of acute RVT superimposed on nephrotic syndrome. When acute RVT arises bilateral, acute decline in GFR and marked oliguric ARF may develop. On the other hand, chronic RVT may frequently be clinically silent. The presence of pleuritic pain or hemoptysis in a patient with NS should alert the clinician to the possibility of RVT and pulmonary emboli. Additional clinical signs of RVT may be back pain, thrombophlebitis in the lower extremity, asymmetric edema, left varicocele, and dilated abdominal veins. Greatly elevated urinary fibrin-fibrinogen products may be helpful in screening for RVT in asymptomatic nephrotic syndrome patients [209, 210].

Color Doppler ultrasound is already the modality of choice for the detection of acute RVT [211, 212]. This noninvasive technique essentially measures the renal venous flow velocity. CT together with intravenous infusion of contrast media also allows a noninvasive evaluation of RVT [213]. Renal magnetic resonance angiography is also a noninvasive method for diagnosing RVT [214]. A major potential advantage in using this technique is the avoidance of iodine contrast media. Confirmation of RVT may be obtained by arteriography with delayed films during the venous phase, by inferior venacavograms, or, preferably, by selective renal venography. However, when renal function is normal, the high rate of renal blood flow leads to a rapid wash out of the contrast media and therefore may render the venography procedure difficult. Digital subtraction venography also seems to be a simple, safe, noninvasive, and quite efficient method to diagnose RVT [215].

Therapy

The treatment of RVT is usually conservative with the use of heparin (clotting time 2 – 2.5 times normal) followed by oral anticoagulation (warfarin) or antiplatelet drugs [216]. Anticoagulation may be of prophylactic value for the occurrence of pulmonary emboli. Additionally, in patients with acute RVT, anticoagulant therapy reduces massive proteinuria and improves renal function in association with demonstrable recanalization of renal veins [217 – 219]. In most cases of chronic RVT, however, anticoagulant therapy has little effect on renal function, and thrombosis may recur in the recanalized veins when the therapy is discontinued. Altogether, the impact on renal function caused by treating asymptomatic chronic RVT is undetermined, but anticoagulation for chronic RVT is associated with relatively few complications [202]. In cases of nephrotic syndrome caused by MN, the anticoagulant therapy should be administered as long as the patient has nephrotic proteinuria, an albumin level < 20 g/L, or both. In patients with other causes of chronic nephrotic syndrome, a more cautious approach may be indicated, and prophylactic anticoagulation should be considered only if the risk of thromboembolism is high [203]. Because of the increased platelet function, platelet-aggregation inhibitors (low-dose aspirin) are a rational choice, although no infor-

mation from controlled studies is available [203].

Thrombolytic therapy (streptokinase, urokinase) can be used safely as long as there are no contraindications. However, this therapy should be reserved for those patients with the most severe disease or worse prognosis and seems to be warranted in the presence of bilateral RVT with ARF, massive clot size with high risk of acute embolic events, or recurrent pulmonary emboli [220 – 222].

The value of surgical thrombectomy in acute RVT has not been determined. However, this procedure may be useful in patients with acute RVT when complications develop such as pulmonary embolism and inferior vena cava thrombosis, right renal vein thrombosis without collateral flow, and acute RVT with shock, and patients are not otherwise expected to survive the acute episode [223].

Whether the high incidence of thromboembolic events in patients with the nephrotic syndrome justifies prophylactic administration of oral anticoagulants remains controversial. A carefully performed Markov-based decision analysis has concluded that for nephrotic patients with MN, the benefits of prophylactic anticoagulation outweigh the risks such as serious bleeding events [224]. However, decision analysis models do not replace the need for prospective, randomized clinical trials. Altogether, it may be prudent, unless contraindicated, to recommend long-term oral anticoagulation to nephrotic patients with MN, when the nephrotic syndrome is anticipated to persist. Additionally, when serum albumin concentration falls < 2.0 – 2.5 g/dL (high risk of thromboembolic events), prophylactic oral anticoagulation seems to be indicated. Also, patients with a history of thromboembolic complications should receive long-term oral anticoagulation. Immobilized nephrotic patients should probably receive short-term, low-dose parenteral heparin during their immobilization followed by oral anticoagulation [224, 225].

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Hereditary, Cystic and Congenital Diseases of the Kidney and the Urinary Tract

Dominique Joly, Shuta Ishibe and Jean-Pierre Grünfeld

The most severe forms of inherited kidney diseases are seen in children, but the most prevalent disorders, such as autosomal dominant polycystic kidney disease, are first seen and managed in adults. All nephrologists are therefore confronted with inherited kidney diseases. Recent progress in molecular genetics has dramatically improved the understanding and classification of these diseases and consequently has made genetic counseling more accurate.

Cystic Kidney Diseases

Please refer to Table 1 for an overview of cystic diseases.

Table 1. Cystic kidney diseases.

Hereditary

Autosomal dominant
- Autosomal dominant polycystic kidney disease
- von Hippel-Lindau disease
- Tuberous sclerosis
- Medullary cystic diseases
- Renal cysts and diabetes
- Glomerulocystic kidney diseases

Autosomal recessive
- Autosomal recessive polycystic kidney disease
- Nephrophthisis
- Meckel-Gruber syndrome
- Bardet-Biedl syndrome
- Zellweger syndrome

X-linked
- Orofaciodigital syndrome, type 1

Chromosome disorders
- Aneuploidies (trisomy 13)

Nonhereditary

Congenital
- Multicystic dysplasia
- Paraplegic cysts
- Medullary sponge kidney

Acquired
- Simple cysts
- Acquired renal cystic disease (chronic renal failure)
- Hypokalemia

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is one of the most common inherited monogenic disorders, occurring in approximately 1 in 600 – 1,000 live births. ADPKD is a systemic disorder characterized by the development of multiple renal cysts, and variably associated with liver, cardiovascular, gastrointestinal, and genital abnormali-

ties. In Western countries, ADPKD accounts for 5 – 10% of end-stage renal disease (ESRD). However, the exact prevalence depends on detection, as the disease is often clinically silent.

Genetics

About 85% of families with ADPKD are linked to the PKD1 locus on chromosome 16 (PKD1 disease). In the remaining families, the genetic defect is linked to the PKD2 locus on chromosome 4 (PKD2 disease). Recent identification of pedigrees unlinked to either of these loci raises the possibility of at least a third locus, yet unmapped (PKD3 disease). De novo mutations probably account for < 10% of all cases of ADPKD. The proteins encoded by PKD1 and PKD2, polycystins 1 (Pc-1) and 2 (Pc-2), are transmembrane proteins that are able to interact, function together as a nonselective cation channel, and also induce several distinct transduction pathways. The "polycystin complex" may have three different subcellular localizations and associated putative functions: at lateral membranes of the cells (with a role in cell-cell interaction); at the basal pole of the cell (with a role in cell-extracellular matrix interaction); at the apical primary cilia of the cells (with a role in the mechanotransduction of the urinary flux) [1]. In ADPKD renal cysts, somatic mutations of the wild-type allele of PKD1 and PKD2 and subsequent loss of the functional polycystin complex presumably trigger a cascade of signaling and gene expression events, ultimately leading to cyst formation.

Renal Pathology

Cyst formation occurs in < 10% of nephrons. Initially, cysts are dilatations of intact tubules, filled by glomerular filtration. Enlarging cysts lose their connection to functioning nephrons. Secretion of fluid into the cysts is responsible for their progressive growth over time, and some kidneys may reach 40 cm in length and 8 kg in weight.

Renal Manifestations of ADPKD

ADPKD often leads to progressive renal failure due, in part, to continued cyst enlargement. Other renal manifestations are flank and abdominal pain, hematuria, urinary tract infection (UTI), nephrolithiasis, and hypertension. Renal cell carcinoma (RCC) is uncommon.

Flank and Abdominal Pain

Flank and abdominal pain, often described as dull and chronic, is the presenting symptom in 20 – 30% of the patients, and its frequency increases with the age as well as with cyst size. Possible mechanisms are stretching of the renal capsule and traction on the renal pedicle. Hepatic cysts may also contribute to right-sided pain. Acute pain suggests a cystic complication (e.g. hemorrhage or infection) or urinary obstruction (e.g. urolithiasis or clot). Nonnarcotic analgesics provide substantial pain relief for the great majority of patients. Analgesic-resistant pain (sometimes severe enough to alter the quality of life) requires evaluation by ultrasonography or computed tomography (CT) scan. Any large cyst detected in the area of pain deserves consideration. Imaging-guided percutaneous aspiration has proved to be minimally invasive and efficient in relieving the pain. Yet, the recurrence of pain is common. The third-line treatment is surgical intervention, either by open surgery or laparoscopic decompression, which is invasive but efficient when applied

to highly selected cases. Cyst decompression does not have any effect on renal function or rate of renal failure progression.

Hematuria

Macroscopic hematuria occurs at some time in the course in 30 – 50% of patients with ADPKD and may be the presenting symptom in 15 – 20%. A precipitating event, such as trauma or strenuous physical activity, is frequently identified. The most likely explanation is rupture of a cyst into the collecting system, but UTI or urolithiasis should be considered. Hematuria usually resolves within a few days with bed rest and hydration to prevent renal colic by clot migration. Blood transfusion or surgical treatment is rarely needed. Some cyst hemorrhage presents with pain but no hematuria, as many cysts do not communicate with the collecting system, in which case CT scan shows a high-density cyst.

Urinary Tract Infection (UTI)

Many ADPKD patients will have one or more UTIs during their lifetime. Lower UTI, infected cyst, and acute pyelonephritis are more likely to occur in women (68%) than men (19%) and can be potentially severe. The initial symptoms of dysuria and frequency, and the presence of Gram-negative enteric bacteria suggest ascending contamination from the bladder. The primary clinical manifestations of renal infection in ADPKD are fever and flank pain. In acute pyelonephritis, urine culture is positive with frequent white cell casts. Bacteremia is rare, and response to conventional antibiotic therapy is good. In cyst infection, a new area of tenderness appears, urine culture is often negative, white cell casts are absent, blood culture is often positive, and response to conventional antibiotic therapy is poor. Hemorrhage into a cyst can mimic infection, with symptoms of pain, transient fever and leukocytosis. Complicated UTI, e.g. associated with a stone, should be excluded by radiologic studies. Patients with renal infection should receive the conventional antibiotic therapy recommended for acute pyelonephritis: third-generation cephalosporin, fluoroquinolones, or trimethoprim-sulfamethoxazole. Short-term aminoglycosides (2 – 3 days) should be reserved for hospitalized patients with severe infection. Fluoroquinolones, or trimethoprim-sulfamethoxazole, are also adequate treatment for cyst fluid infection, because they easily diffuse into the cysts. The duration of therapy ranges from 10 – 20 days, but some patients with presumed infection of a cyst have been treated for as long as 4 – 6 weeks [2].

Nephrolithiasis

Kidney stones occur in up to 20% of patients with ADPKD. In contrast to the predominance of calcium oxalate in idiopathic stone formers, more than one-half of stones in ADPKD are composed of uric acid. Both mechanical changes induced by the large cysts and metabolic abnormalities may contribute to stone formation. These abnormalities include low urinary pH, hypocitraturia and, less often, hyperuricuria and hypercalciuria. Establishing the diagnosis by ultrasonography is more difficult than in idiopathic stone formers because of the large cysts and possible calcifications in cyst walls. CT scanning has good sensitivity for the detection of small or radiolucent stones. The treatment of obstructing stones is more difficult than in patients with idiopathic stone disease. Percutaneous nephrostomy and extracorporeal shock-wave lithotripsy have both been used successfully [3].

Hypertension

Hypertension is a common and early finding in ADPKD, occurring in 33% of the patients with normal renal function and in up to 80% of patients with renal failure. Affected children or young adults may have a higher blood pressure and a higher left ventricular mass index when compared with age-matched unaffected relatives. Renin release in areas of renal ischemia around growing cysts and extracellular volume expansion may play an important role in hypertension. The main objective of antihypertensive treatment in ADPKD patients is to prevent cardiovascular complications. Mean blood pressure is less correlated to the rate of progression of renal failure than in other nephropathies, although the usefulness of an early intervention has not been tested. In some ADPKD patients (usually with massive cystic disease), ACE inhibitors may induce an early and reversible decline in glomerular filtration rate (GFR). However, these drugs, like any other antihypertensive agents, may be used in ADPKD, provided their dosage is adjusted to the degree of renal insufficiency [4].

Chronic Renal Failure

Progressive renal failure is frequent in ADPKD. Recent studies suggest that only $^1/_4$ – $^1/_2$ of the patients with ADPKD will survive without ESRD. When renal failure develops, mean GFR decline is 6 ml/min/year. ESRD is typically reached at 55 years of age, and 75% of the patients start regular dialysis between ages 40 and 60. ESRD is very rare among ADPKD children, and the likelihood of requiring dialysis is < 5% under age 40 and 20% after 60. However, precise individual prediction of renal prognosis is difficult, because there is little intrafamilial concordance. The main determinants of progression are

- sex: males reach ESRD 5 – 6 years before females;
- genotype: PKD2 disease is less aggressive than PKD1, with ESRD occurring later (69 vs. 55 years);
- black race, especially if sickle cell trait is present. Low-protein diet or ACE inhibitors do not reduce the rate of progression of renal failure [5].

Renal Cell Carcinoma (RCC)

RCC is a rare complication among ADPKD patients, occurring with the same frequency as in the general population. However, tumors are more often bilateral at presentation, multicentric, and sarcomatoid in type. The diagnosis of von Hippel-Lindau disease (vHL) (see below) should be considered in any polycystic patient with bilateral RCC.

Extrarenal Manifestations of ADPKD

ADPKD is frequently associated with cysts in the liver (and occasionally pancreas or spleen), and this finding can help in confirming the diagnosis. Other abnormalities, both vascular and extravascular, are consistent with a generalized dysfunction of extracellular matrix or epithelial cell differentiation.

Liver Cysts

Liver cysts develop later than renal cysts; they are very rarely found before 20 years of age and their prevalence reaches 80% after 60 years of age. The cysts, which appear to be derived from biliary epithelium, are more commonly seen in patients with advanced renal disease. They are more prevalent and are

observed earlier and more extensively in females than in males. Most patients remain asymptomatic with preserved hepatic function. Persistent and severe pain may require cyst decompression. Cyst infection is rare, occurring mainly in dialysis or transplant patients, and requires antimicrobial therapy with occasional percutaneous drainage.

Massive polycystic liver may lead to gastrointestinal tract compression with abdominal pain. Posterior cysts may compress the suprahepatic veins and intrahepatic vena cava, resulting in portal hypertension and ascites. Percutaneous puncture and sclerosis (with alcohol or minocycline), laparoscopic fenestration, partial hepatic resection and even liver transplantation have been attempted with some success in these patients [6].

Intracranial Aneurysms

The prevalence of asymptomatic intracranial aneurysm in ADPKD patients has been found to be approximately 8%, compared to 1.2% in the general population. The rupture of an intracranial aneurysm, resulting in subarachnoid or intracerebral hemorrhage, is the most serious complication in ADPKD, as death or severe disability occurs in 50% of cases. The risk is 2 – 4 times greater in patients who have a positive familial history of intracranial aneurysm. Mean age at rupture is 41 years, with 10% of the patients being less than 21 years of age. One half of patients have normal renal function at this time. In $^1/_3$ of the cases, rupture is preceded by premonitory symptoms, e.g. unusual headaches, often acute and posterior. Patients with ruptured aneurysm should be managed in a neurosurgical unit. Non-enhanced CT scanning is the first-line diagnostic procedure, detecting both the aneurysm and blood in the cerebrospinal fluid. If CT scan is negative, a lumbar puncture should be performed to look for the presence of red blood cells, followed by arteriography. The middle cerebral artery is usually involved, and some patients have multiple aneurysms.

Should asymptomatic ADPKD patients be screened for intracranial aneurysm? At present, routine screening is recommended only for selected patients: those with previous rupture, positive family history of aneurysm, a high-risk occupation, and before major elective surgery. The issue of screening in other ADPKD patients is still unresolved. Spiral CT scanning and, preferably, magnetic resonance angiography are the two major screening procedures able to detect small aneurysms (5 mm in diameter). The indications for prophylactic treatment (surgery or radiologic intervention) depend on the size, number, and location of the detected aneurysm(s). If observation is elected, a second radiological evaluation should be performed 6 – 12 months later. If screening is negative in an at-risk patient, tests should be repeated every 3 – 5 years, as cerebrovascular disease is progressive [7].

Cardiac Valve Disease

Mitral valve prolapse and aortic regurgitation are detected by cardiac ultrasonography in up to 30% of patients with ADPKD, a rate 10 times that of the general population. Mitral regurgitation and aortic root dilatation are less frequent. The vast majority of these lesions are asymptomatic but may progress over time and become severe enough to require valve replacement. Antimicrobial prophylaxis is mandatory whenever murmurs are audible. Aortic and coronary aneurysms and dissection of cervical arteries have occasionally been reported.

Table 2. Diagnostic criteria of overt ADPKD (PKD1 disease).

Positive family history, with an autosomal dominant inheritance pattern

– Ultrasonography of patient's parents may help establish autosomal dominant inheritance if family history negative.

*Enlarged kidneys with multiple bilateral renal cysts on ultrasonography (or CT scanning)**

– patients < 30 years
  2 cysts (unilateral or bilateral)
– patients aged 30 – 59
  2 cysts in each kidney
– patients > age 60
  4 cysts in each kidney

Direct genetic testing (mutation identification) or indirect genetic testing (linkage analysis) are not routinely performed in ADPKD.

*In difficult cases, demonstration of cysts in the liver, pancreas, and spleen is useful.

Digestive Abnormalities

Colonic diverticula is a frequent finding in ADPKD patients with ESRD. The frequency of umbilical and inguinal hernias is increased in ADPKD.

Diagnosis and Screening of ADPKD

The diagnosis is usually easy to establish in overt disease, since most patients present with a familial history of ADPKD and enlarged kidneys with multiple bilateral cysts on ultrasonography [8] (Table 2).

Cyst formation can rarely be detected during fetal life. In PKD1 disease, 8% of children < 10 years old have cysts demonstrated by ultrasonography. This probability increases to virtually 100% by the age of 30. A negative ultrasound cannot definitely exclude the disease until the patient is older than 30, although the false negative rate at age 20 is only about 4%. Since symptomatic disease is relatively uncommon in young children, ultrasound screening is usually not recommended before the age of 18. These criteria (Table 2) do not apply to patients with the PKD2 disease, who form cysts at a later age, have a slow rate of progression, and a low risk for renal failure.

A case for precise presymptomatic screening is the young adult who is a potential renal transplant donor. If ultrasonogram is negative, genetic linkage analysis may be indicated.

Pregnancy

Information on the specific risks during pregnancy should be provided. Although normotensive ADPKD women usually have successful and uncomplicated pregnancies, the relative risks of hypertension (16%) and preeclampsia (10%) are 2.5 times greater than in the general population. ADPKD women with preexisting hypertension are at high risk for fetal and maternal complications [9].

Renal Replacement Therapy

When ESRD is reached, maintenance hemodialysis is initiated. The tolerance of this treatment has been found to be even better in ADPKD patients than in patients with other renal diseases, possibly because of less severe anemia, at least before the introduction of recombinant human erythropoietin (rHu-EPO). Peritoneal dialysis is not advisable in patients with very large polycystic kidneys. Kidney transplantation should be considered in patients who are < 65 years old, provided that careful cardiovascular work-up is performed in older patients. Elective nephrectomy, uni- or bilateral, is advised when kidney size is an

obstacle to transplantation or when recurrent renal infection or gross hematuria has occurred. The results of transplantation are similar to those obtained in patients with other renal diseases and similar ages. ADPKD itself has no negative impact on overall survival in renal replacement therapy. Liver cysts are rarely symptomatic. The incidence of major valvular heart disease is not strikingly increased when compared to the general population of patients in renal replacement therapy [10].

von Hippel-Lindau Disease (vHL)

vHL is transmitted as an autosomal dominant trait. Individuals inheriting a mutant vHL gene are predisposed to develop hemangioblastoma of the cerebellum, brain stem, spinal cord, and retina; renal cysts and cancers; pheochromocytoma; pancreatic cysts and carcinoma; and epididymal cystadenoma. In a vHL family, diagnosis can be made if an individual develops one of the above cardinal manifestations (except renal cysts). In the absence of a typical familial history, two cardinal manifestations must be present, including hemangioblastoma of either the retina or central nervous system.

The vHL gene has been localized to chromosome 3p25-26, and acts as a tumor suppressor gene. Tumor formation depends on the so-called "2-hit" theory of Knudson. One copy of the vHL gene is mutated in the germline of vHL patients (first hit), and a somatic inactivation of the second copy (second hit) initiates tumorigenesis. Cells lacking vHL protein overproduce products of the hypoxia inducible factor (HIF), such as vascular endothelial growth factor (VEGF) or transforming growth factor (TGF) [11].

Identification of the germline vHL mutation in a given vHL family is useful. Any at-risk member of this family should be tested for this mutation. If negative, no further medical testing is necessary; if positive, periodic testing for occult manifestations of vHL disease is highly recommended.

Renal involvement in vHL disease is characterized by multiple and bilateral renal cysts and renal cell carcinomas (RCC) with increasing frequency as the patient ages. It is estimated that cysts will develop in 95% and RCC in 70% of patients who survive to age 80. Cysts typically appear earlier than RCC; the youngest reported patient with RCC was 16 years old. In at-risk individuals above this age, annual renal ultrasound screening should be performed and, if abnormal, should be complemented with RMI or CT scan.

Typical cysts cause few problems. RCC is of greater concern, accounting for more than 25% of deaths in vHL patients. Renal-sparing surgery, e.g. tumorectomy or partial nephrectomy, whenever possible, provides safe and effective treatment for RCC in vHL patients. This conservative approach, rather than total nephrectomy, has been advocated to delay ESRD. Surgery is recommended when the diameter of the largest solid tumor is above 2.5 – 3 cm; only atypical cysts should be removed. Tumors recur in approximately 30% of patients at five years after surgery and 85% at 10 years, leading to repeated surgery. Renal failure in vHL patients is mainly related to repeated surgeries with parenchymal resection. ESRD due to cysts and infiltrative RCC is rare. Some vHL patients with RCC but no metastasis have now undergone kidney transplantation 1 – 2 years after bilateral nephrectomy [12].

Tuberous Sclerosis (TS)

TS (also called Bourneville's disease) is a rare autosomal dominant disease. Its preva-

lence ranges from 1/5,800 – 1/14,500. Familial history is often negative, mainly because of the high incidence of de novo mutations (60 – 70%), and variable penetrance of the genetic defect in the remaining cases. Two different genes can cause the disease: TSC1 (encoding hamartin), localized to chromosome 9q34, and TSC2 (encoding tuberin), localized at 16p13 and adjacent to the PKD1 gene. TSC1 and TSC2 act as tumor suppressor genes.

Extrarenal lesions of TS involve central nervous system cortical tubers, subependymal nodules, calcifications and astrocytoma and retinal hamartoma; hypopigmented spots on the trunk, facial angiofibroma, ungual fibroma (Koenen tumors), café-au-lait spots, shagreen patch and molluscum fibrosum pendulum of the skin; rhabdomyoma; and, rarely, pulmonary lymphangiomyomatosis.

Kidney involvement is also inconstant. The most common and characteristic renal lesions are multiple and bilateral angiomyolipomas. These benign tumors often grow over time and may require surgery or embolization if larger than 4 cm, symptomatic, or complicated by bleeding. Bilateral renal angiomyolipomas make the diagnosis of TS highly probable, whereas a single solitary lesion is very common in the general population. Some patients present with multiple growing cystic lesions, similar to those seen in ADPKD, with potential complications such as pain, bleeding into the cyst, hematuria, hypertension, and progressive renal failure. Some of these patients have a chromosomal deletion including both the TSC2 and PKD1 genes ("contiguous gene" syndrome). Patients with TSC1 disease do not form cysts. RCC is found in < 5% of patients, but should be considered if periodic ultrasonography or CT scanning shows any atypical cyst or angiomyolipoma. Finally, focal segmental glomerular sclerosis, interstitial fibrosis, small kidneys, and ESRD have been reported in a few patients [13].

Medullary Cystic Kidney Diseases

Autosomal dominant medullary cystic kidney disease (MCKD) and familial juvenile nephrophthisis (NPHP) have for many years been described together as the NPHP-MCKD complex. However, MCKD mainly affects adults and is inherited with an autosomal dominant mode, while NPHP mainly affects children or young adults and is inherited with an autosomal recessive mode (see below). Recent research has also shown that these two entities are genetically different. Moreover, it now appears that two different genes are responsible for MCKD.

Medullary Cystic Kidney Disease Type 1 (MCKD1)

Patients with MCKD1 have few symptoms, except for early polyuria and polydipsia related to renal salt wasting in some cases. In the early stages of the disease, renal cysts are absent in 50% of the patients on ultrasonography. Medullar cysts become apparent in most of the patients in advanced stages and towards ESRD, reached at a median age of 62 years. MCKD1 locus has been mapped on chromosome 1q23.1 [14].

Medullary Cystic Kidney Disease Type 2 (MCKD2) and Familial Juvenile Hyperuricemic Nephropathy (FJHN)

MCKD2 and FJHN were initially described separately; they share many features, includ-

ing polyuria, progressive interstitial fibrosis with renal failure, hyperuricemia, and gout. Corticomedullary cysts are well-documented in MCKD2, but their presence in FJHN is not well-documented. However, it is now clear that these two diseases form the same entity. MCKD2 and FJHN result from allelic mutations of a common gene, UMOD, which codes for uromodulin (or Tamm-Horsfall protein), the most abundant protein in normal urine.

Renal Cysts and Diabetes Syndrome (RCAD)

Heterozygous mutation in the gene encoding hepatocyte nuclear factor (HNF)-1 , a DNA transcription factor, was initially described as one of the main molecular causes of maturity-onset diabetes of the young (MODY). It now appears that renal anomalies are the key feature of HNF-1 phenotype and often precede the onset of diabetes. Renal cysts and progressive renal failure are frequent; glomerulocystic kidney disease and renal hypoplasia have been reported. Abnormal liver function tests, hyperuricemia and urogenital malformations have also been related to HNF-1 mutations [15].

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is a rare condition, with an estimated prevalence of 1 : 20,000 live births. Renal cysts develop only from the collecting ducts, and are constantly associated with a hepatic lesion, congenital hepatic fibrosis, or fibroadenomatosis. Mutations at a single locus, polycystic kidney and hepatic disease 1 (PKHD1), are responsible for all typical forms of ARPKD. The PKDH1 gene product, fibrocystin, is a transmembrane protein localized to the cell primary cilia.

The clinical spectrum is variable and correlated to the severity of mutations. Up to 50% of affected neonates will die soon after birth from pulmonary hypoplasia, caused by abdominal distension and enlarged kidneys. Other neonates will survive and during childhood will eventually develop recurrent UTIs, severe hypertension, and fluctuating renal failure. With hypertension control, 50% of the children may reach adulthood without the need for renal replacement therapy.

Congenital hepatic fibrosis is a constant finding and may be the predominant clinical feature. This hepatic disease may either be asymptomatic or cause portal hypertension and bacterial angiocholitis, if intrahepatic ducts are dilated. Liver function tests are usually normal. Ultrasonography of the liver may reveal dilated bile ducts, hepatic cysts, and portal hypertension.

Because of increased use of ultrasonography in the fetus, pediatricians may be confronted with the discovery of bilateral renal cysts. In very rare cases (100 in the literature), ADPKD (PKD1 form or in association with TSC2) may manifest early, leading to ESRD in the very first years of life. The diagnosis of the cystic disease is then based on the result of ultrasound in the parents. The presence of renal cyst in one parent supports ADPKD. In contrast, ARPKD is suggested when both parents have no cysts and when the liver lesion is detected in the proband. High intrafamilial variability in ARPKD disease expression should be underlined; disease expression is often different among siblings. Every older asymptomatic sibling of affected children should be evaluated for hepatic fibrosis [16].

Nephrophthisis (NPHP)

NPHP is a group of autosomal recessive tubulointerstitial nephropathies with multiple small medullary cysts. NPHP is the most common genetic cause of ESRD in children and young adults. 15% of patients have no obvious family history. These apparently sporadic cases are not surprising in an autosomal recessive disorder. 80% of NPHP cases are caused by homozygous deletions of the NPH1 gene, which codes for nephrocystin. At least three other genes (NPH2, 3 and 4) account for the remainder of the cases, and the respective encoded proteins (inversin, nephrocystin 3, nephrocystin 4) may interact in common signaling pathways downstream the primary cilia of the cells [17, 18].

Polyuria, polydipsia, growth retardation, and urinary sodium leak are present in children between 1 and 3 years of age. Proteinuria is a late finding. Renal failure appears before 12 years of age in most cases and uniformly progresses to ESRD before 20, with a mean age of 14 years. At ultrasound examination, kidneys have a normal or slightly reduced size with smooth outline, increased echogenicity, and loss of corticomedullary differentiation. Multiple small or large cysts at the corticomedullary junction are usually seen in advanced renal failure. CT scanning is more sensitive, detecting cysts as small as 5 mm in diameter. Histology shows small cysts (1 – 10 mm) irregularly distributed at the corticomedullary junction and in the medulla, arising from intact distal and collecting tubules. Medullary cysts appear later in the course and are often absent in renal biopsies performed at an early stage. On light microscopy, atrophic tubules alternate with groups of dilated or collapsed tubules. Changes in tubular basement membranes, including homogeneous or multilayered thickening and disintegration, are highly suggestive of NPHP. There is moderate interstitial fibrosis with rare inflammatory cells.

Detection of NPH1 homozygous deletions allows diagnosis for the propositus and siblings, and prenatal diagnosis without the need for renal biopsy. Therapy for NPHP is exclusively symptomatic. The tubular injury does not recur in the transplanted kidney.

Many eye anomalies have been reported in association with NPHP. Senior-Loken syndrome (not linked to NPH1) is defined by the combination of a NPHP phenotype with tapetoretinal degeneration (18% of NPHP cases). Leber's congenital amaurosis is the early-onset form, with children being blind from birth. In the late-onset form, blindness develops subsequently. Cerebral disease, e.g. mental retardation and cerebellar ataxia, various bone anomalies, and hepatic fibrosis have been described in some families [19].

Hereditary Diseases

A classification of hereditary noncystic disease can be found in Table 2.

Alport Syndrome

Alport syndrome is a hereditary hematuric glomerular disease progressing to ESRD in males, often associated with hearing loss and specific ocular changes. The prevalence of Alport syndrome is 1/5,000 and it accounts for 2% of ESRD. The disease is clinically and genetically heterogeneous. Defects in type IV collagen are responsible for the disease. Genes coding for the different chains of this essential component of basement membranes have been cloned, and mutation characterization has made genetic counseling possible (see Table 4).

Table 3. Main renal hereditary diseases (non-cystic).

Predominant glomerular involvement
- Alport syndrome
- Hereditary nephritis with macrothrombocytopenia
- Congenital nephrotic syndrome of Finnish type
- Familial steroid-resistant FGS
- WT1-related glomerulopathies (Denys-Drash syndrome, diffuse mesangial sclerosis, Frasier syndrome)
- Nail-patella syndrome
- Metabolic disorders
  - Fabry disease
  - LCAT deficiency
  - Glycogenosis, type 1
  - Hereditary amylosis
- Primitive glomerulopathies, sometimes familial (IgA, collagen III, fibronectin)

Predominant tubular involvement

Fanconi syndrome
- *Idiopathic*
- *Secondary* (cystinosis, Wilson's disease, Lowe syndrome, galactosemia, tyrosinemia, fructose intolerance, type I glycogenosis, mitochondrial cytopathies, etc.)

Other tubular diseases
- Bartter syndrome
- Gitelman syndrome
- Liddle syndrome
- Pseudohypoaldosteronism, type I
- Pseudohypoaldosteronism, type II
- Nephrogenic diabetes insipidus

Hereditary urolithiasis
- Cystinuria
- Hyperoxaluria, primitive
- Renal tubular acidosis
- ARTPase deficiency
- Dent's disease

Various malformative syndromes with renal involvement
- Branchiaotorenal syndrome
- Bardet-Biedl syndrome

Clinical Symptoms and Course

In 80 – 85% of kindreds, this disorder is inherited as an X-linked trait. Pedigree analysis shows two important clinical characteristics: father-to-son transmission does not occur, and males are severely affected, while females tend to have a benign course. The initial renal manifestations in males may be recurrent episodes of gross hematuria precipitated by upper respiratory infections during childhood and adolescence. Microscopic hematuria begins in the first years of life. Proteinuria develops later and increases with age, sometimes reaching the nephrotic range. Progressive renal failure and hypertension occur with time. ESRD affects virtually all males before age 30 (juvenile form), but in some families is delayed until age 45 – 70 (adult form). The rate of progression to renal failure is quite constant in males within the same family, but some intrakindred variability has been reported in adult forms. Women are heterozygous, and carriers tend to have a benign course, with 90% having microscopic hematuria during pregnancy or familial screening. However, 10% of them will develop late ESRD, sometimes predicted by gross hematuria during childhood, nephrotic syndrome, and diffuse glomerular damage on electron microscopy examination.

Sensorineural hearing loss occurs in more than 50% of affected males and begins around 10 years of age, with bilateral hearing defect involving high tone frequencies (4,000 to 8,000 Hz) detected by audiometry. Often the hearing defect is moderate and nonprogressive in adults. When present, this symptom frequently shares renal involvement in precocity and severity. Women are less frequently affected, and hearing loss may develop later in life. Ocular defects are less common than hearing loss (15 – 30% of patients). Anterior lenticonus (conical protru-

Table 4. Alport syndrome and related diseases.

Clinical definition	Biochemical defect	Genetic defect
X-linked (classical)	5 (IV)	COL 4 A5
X-linked with leiomyomatosis	5 (IV) and 5 (IV)	COL 4 A5 and COL 4 A6
Autosomal recessive	3 (IV) or 4 (IV)	COL 4 A3 or COL 4 A4
Autosomal dominant	3 (IV) or 4 (IV)	COL 4 A3 or COL 4 A4

5 (IV): -5-chain of type IV collagen
COL 4 A5: gene encoding for

sion of the lens into the anterior chamber) usually develops after 20 years of age. It is pathognomonic of Alport syndrome and strongly correlates with severe nephritis, although it has also been described in females with milder disease. It may be accompanied by severe myopia and opacities of the lens. Other ocular lesions have been reported, such as whitish or yellowish perimuscular lesions in the retina or recurrent corneal ulcers.

Diffuse leiomyomatosis involving the esophagus, tracheobronchial tree, and female genitalia have been reported in more than 20 families. Diffuse leiomyomatosis is inherited as an X-linked dominant trait. Affected females have leiomyomatosis and are carriers for hereditary nephritis. Dysphagia, epigastric pain, vomiting, bronchitis, stridor, and cough appear before adolescence, and imaging (MRI or CT scan) helps to confirm the suspected leiomyomatosis.

Autosomal recessive inheritance accounts for 15 – 20% of cases of Alport syndrome. In this setting, Alport syndrome is often juvenile and severe, with constant hearing loss and very frequent ocular lesions. Women are as severely affected as males in the same kindred. Parents without severe nephropathy and parental consanguinity highly suggest recessive transmission. Autosomal dominant Alport syndrome is very rare.

Renal Pathology

When Alport syndrome is suspected, renal biopsy must focus on ultrastructural and immunological analysis of glomerular basement membranes (GBM). The changes on light microscopy or direct routine immunofluorescence provide prognostic clues, but are nonspecific: focal increased glomerular cellularity, glomerulosclerosis, and interstitial infiltrate containing lipid-laden foam cells. The earliest change is thinning of the GBM (which is not pathognomonic). With time, changes become diagnostic for hereditary nephritis, with the development of longitudinal splitting of the GBM on electron microscopy, producing a multilamellated thickened appearance. Cycles of injury-repair of the GBM may be responsible for these changes. In males, the number of glomeruli showing splitting increases with age to reach 90% by age 30.

Immunohistochemistry is a useful adjunctive study, because antibodies directed against the different chains of type IV collagen have become available. It must be remembered that a normal chain expression does not exclude Alport syndrome. Antibody staining will always be absent with large defects (gene deletion), but some point mutations might result in antigenicity normal but

functionally abnormal (IV) chain formation. Thus, antibody staining might be relatively normal, falsely suggesting that the patient does not have hereditary nephritis.

In X-linked Alport syndrome in males, absence of 3, 4 and 5 (IV) in GBM, tubular basement membrane, and Bowman's capsule is diagnostic, while women frequently show mosaic expression of these chains. In the autosomal recessive form, 3, 4, and 5 are not detected in the GBM while 5 is still present in the basement membrane of the collecting duct and skin where 3 and 4 are not normally expressed. Examination of skin biopsies for 5 (IV) expression is an additional tool, because this chain is normally expressed in the epidermal basement membrane. Lack of its expression is diagnostic in a male with suspected Alport syndrome and may preclude the need for renal biopsy. Here again, a normal expression does not exclude the diagnosis. In heterozygous women, the 5 expression pattern may be mosaic, diagnostic of a carrier state, or normal, e.g. non-diagnostic.

Pathogenesis

Type IV collagen is ubiquitously present in basement membranes. Type IV collagen molecules self-associate into polygonal networks and interact with several glycoproteins to form basement membranes. Each type IV collagen molecule is composed of three -chains. Six different -chains (1 – 6) have been identified and their genes recently cloned.

The six type IV collagen genes are arranged in pairs on three different chromosomes: 1- and 2- (IV) chains are encoded by COL4A1 and COL4A2 genes on chromosome 13; 3 and 4 (IV) are encoded by COL4A3 and COL4A4 genes on chromosome 2; 5 and 6 (IV) are encoded by COL4A5 and COL4A6 genes on chromosome X. Expression of the various type IV collagen chains, as determined by antibodies staining, shows that 1 and 2 (IV) are present in all basement membranes, while 3 and 4 have restricted distribution, including basement membranes involved in Alport syndrome (GBM, lens capsule, and cochlea). All basement membranes that express 3 and 4 (IV) also express 5 (IV), and suggest a preferential 3 4 5 network formation.

A mutation affecting one of the chains involved in the putative 3 4 5 network can not only prevent GBM expression of that chain, but also that of the other 2 chains as well. The network is usually absent from Alport patients' basement membranes or sometimes persists with probable defects in structure and function. How the basement membrane defects produce clinical disease remains unclear. High glomerular capillary pressure might directly damage a weakened GBM. Alternatively, defective synthesis of the (IV)-chain may promote the synthesis of other types of collagen, leading to glomerulosclerosis. It is likely that abnormal collagen IV function is also responsible for the extrarenal manifestations in hereditary nephritis.

Not surprisingly, in more than 50% of X-linked Alport syndrome families, mutations (90%) or major rearrangements (10%) of the COL4A5 gene have been identified. These mutations are likely to interfere with the normal folding of the 5-chain into triple helices with other (IV). The variability in clinical course may result, at least in part, from different mutations in the 5 gene. Affected males with a gene deletion may have more severe disease than those with a point mutation. Patients with leiomyomatosis show deletions at the 5' ends of both the COL4A5 and COL4A6 chains (located head-to-head on the X chromosome). In autosomal reces-

Table 5. Genetic counseling in Alport syndrome.

– Identify the mode of inheritance in a given family. X-linked dominant (more than 80% of cases) Autosomal recessive (rarely dominant)
– Characterize the mode of progression in affected males with X-linked disease. Juvenile vs. adult type
– Identify carrier heterozygous females in X-linked disease. Clinical diagnosis (may be uncertain) Molecular diagnosis: identification of the mutation in the family [5 (IV)] or linkage analysis
– Provide information to the patients and families, including risk of progression and transmission to offspring

sive Alport syndrome, mutations of either COL4A3 and/or COL4A4 have been described. In autosomal dominant Alport syndrome, COL4A4 mutations (with a possible dominant negative effect) have been described.

Genetic Counseling

The principal steps are summarized in Table 5 [20].

Differential Diagnosis

Alport syndrome is usually suspected from the family history of renal failure and deafness. In this setting, other major causes of persistent glomerular hematuria are unlikely. In up to 15% of cases, there is no family history of renal disease, and the diagnosis is first suggested by renal biopsy. These patients probably represent new mutations (10 – 15% of cases) in the gene responsible for the basement membrane abnormalities.

Treatment

There is no specific treatment for hereditary nephritis. ACE inhibitors reduce protein excretion in some patients and may slow renal failure in male patients with hypertension and progressive disease. Dialysis or transplantation can be performed in those patients with hereditary nephritis who develop ESRD. Initial disease does not recur in the transplant, but some patients develop anti-GBM antibody disease. These antibodies are directed against the Goodpasture antigen (within the 3-chain). This epitope is recognized as foreign in the graft because it is not expressed in the native kidneys. The incidence of anti-GBM antibody disease in the transplant is not known, because antibody deposition has been found in patients with and without clinical disease. Less than 5% of transplanted patients will develop early clinical disease with crescentic glomerulonephritis and frequent loss of the graft despite plasmapheresis and immunosuppressive treatment. The risk factors for this complication are juvenile renal failure, large gene deletions, and first graft loss due to anti-GBM antibody disease [21].

Hereditary Nephritis with Macrothrombocytopenia

More than 30 families with autosomal dominant transmitted hereditary nephritis, deafness cataract, and hematologic abnormalities have been reported under the terms of either Epstein syndrome or Fechtner syndrome

and were considered to be Alport syndrome variants. Hematologic findings include macrothrombocytopenia (low platelet count and giant platelets) and leukocyte inclusions, known by hematologists under the names of May-Hegglin syndrome or Sebastian syndrome. These four syndromes result from allelic mutations of a common gene, MYH9, which codes for the heavy chain of non-muscle myosin IIA, an enzyme linked to the cytoskeleton [22]. There is considerable intrafamilial phenotypic variability, and in some kindreds, males present with hematologic abnormalities but no renal involvement.

Congenital Nephrotic Syndrome of Finnish Type (CNF)

CNF is the leading cause of congenital nephrotic syndrome. CNF is frequent in Finland, with an incidence of 1 in 8,000 births, but has also been described all-around the world. CNF is inherited as an autosomal recessive trait. Heterozygous individuals do not manifest renal disease. The responsible gene, NPHS1, codes for a novel immunoglobulin-like protein, nephrin, which is responsible for the intercellular adhesive force between podocytes at the glomerular slit diaphragm [23]. Nephrin mutations result in truncated proteins that alter the glomerular filtration barrier and cause the nephrotic syndrome. Two major nephrin mutations (Fin-major and Fin-minor) account for more than 94% of the CNF in the Finnish population (suggesting a founder effect), but are rare in non-Finnish patients.

CNF becomes overt during early fetal life (15 weeks) with fetal proteinuria, high amniotic fluid, and maternal plasma -fetoprotein (AFP) concentration. In at-risk families, these changes used to lead to termination of the pregnancy, but today NPH1 gene analysis is the method of choice to establish a precise prenatal diagnosis.

Most infants with CNF are born prematurely with a low weight for gestational age. Fetal distress is not uncommon. In 50% of cases, edema is discovered during the first week of life. Highly selective proteinuria without hematuria, hypoalbuminemia, normal renal function, and enlarged, hyperechogenic kidneys without normal corticomedullary differentiation are the initial findings. Renal biopsy shows mild mesangial changes of hypercellularity and increased matrix, without any immune deposits on immunofluorescence studies. Over time, progressive glomerulosclerosis, tubulointerstitial changes, and fibrosis develop. As the disease progresses, growth retardation, bacterial infections, thromboembolic complications, and hypothyroidism may occur. ESRD invariably develops before 8 years of age.

CNF is not an immunologic disease and is always resistant to corticosteroids and immunosuppressive drugs. Treatment is conservative and includes albumin infusion, -globulin replacement, nutrition with a high-protein and low-salt diet, tube feeding or parenteral alimentation, vitamin and thyroxine substitution, and prevention of infections and thrombotic complications. The combination of an ACE inhibitor and indomethacin to reduce intraglomerular pressure and lower protein excretion may improve both nutritional status and growth and may obviate the need for bilateral nephrectomy. Dialysis is begun when ESRD is reached. Renal transplantation is considered when a sufficient body weight (8 – 9 kg) is reached. The disease does not recur after transplantation. Interestingly, recent reports suggest that minor mutations of nephrin could be responsible for milder or atypical forms of nephrotic syndrome in children.

Familial steroid-resistant Focal Segmental Glomerulosclerosis (FGS)

NPHS2 gene, which encodes podocin, was found to be mutated in some families with recessive steroid-resistant nephrotic syndrome [24]. In these families, the nephrotic syndrome ranges from early onset (resembling CNF) to a late onset, in the second decade of life, resembling idiopathic FGS. Not surprisingly, podocin mutations were also detected in rare cases of sporadic steroid-resistant nephrotic syndrome [25].

Mutations in ACTN4, encoding -actinin-4, cause autosomal dominant focal segmental glomerulosclerosis [26].

Podocin and -actinin-4 are both synthesized and exclusively expressed by the podocytes. Podocin is an integral membrane protein with a short extracellular domain and may connect the slit diaphragm to podocyte cytoskeleton. -actinin-4 is an actin-filament crosslinking protein. These two proteins may interact with nephrin in a network regulating podocytes plasticity and slit diaphragm permselectivity.

WT1-related Glomerulopathies

WT1, the Wilms' tumor suppressor gene, encodes a transcription factor that regulates the expression of many genes and plays a major role in renal and genital development. WT1 complete deletions are responsible for WAGR syndrome (Wilms' tumor, Aniridia, Genitourinary malformations, Mental retardation); WT1 germline truncations are found in 10% of Wilms' tumors; and finally, WT1 point mutations have been detected in three disorders with predominant glomerular involvement. Most of these WT1 mutations arise de novo and have a dominant effect [27].

Denys-Drash Syndrome

This syndrome is characterized by the combination of diffuse mesangial sclerosis, male pseudohermaphroditism, and Wilms' tumor. Denys-Drash syndrome is usually sporadic, but constitutional mutations in the Wilms' tumor predisposing gene WT1 have been found. The clinical course of the nephropathy is not different from that described above in isolated diffuse mesangial sclerosis (see below). Wilms' tumor (unilateral or bilateral) may be the first clinical manifestation of the syndrome. Male pseudohermaphroditism is characterized by ambiguous genitalia or female phenotype with a 46, XY karyotype.

Isolated Diffuse Mesangial Sclerosis (IDMS)

Diffuse mesangial sclerosis is the leading cause of infantile nephrotic syndrome. Children are usually normal at birth. Proteinuria with an unremarkable urine sediment develops postnatally and increases during the first 2 years of life. In rare cases, however, the nephrotic syndrome may be present at birth or even be suspected in utero because of elevated maternal plasma AFP and enlarged and hyperechogenic fetal kidneys. Most children develop hypertension, and all progress to ESRD before age 3. The mesangial sclerosis is initially characterized by a progressive increase in mesangial fibrillar matrix and cells. Capillary lumens are then reduced, and the glomerular tuft contracts into a sclerotic mass within a dilated urinary space, with thickening of the GBM. Mesangial and perglomerular nonspecific immune deposits (IgM, C3 and C1q) are common. Diffuse mesangial sclerosis is resistant to steroids and immunosuppressive therapy. The nephrotic

syndrome is mild, and supportive treatment is less aggressive than in CNF. Recurrent disease does not develop in the transplanted patient. Extrarenal symptoms have been reported, including mental retardation, microcephaly, muscular dystrophy, and various ocular anomalies. The disease is transmitted as an autosomal recessive trait. WT1 mutations have only been detected in 15% of IDMS cases, suggesting genetic heterogeneity. From a practical point of view, every patient with suspected IMDS should be screened for the Denys-Drash syndrome and would benefit from a karyotype (if phenotypically female) and an ultrasonography to detect potential Wilms' tumor [28].

Frasier Syndrome

This rare syndrome, caused by a specific intronic mutation of the WT1 gene, was initially characterized by male pseudohermaphroditism, the absence of Wilms' tumor, and a slowly progressive glomerulopathy. The proteinuria appears in the first decade and increases with age, resulting in steroid-resistant nephrotic syndrome, and ultimately ESRD by age 6 – 35. Renal histology shows normal glomeruli or FGS. All patients have female external genitalia. Theoretically, this rare diagnosis should be suspected in every young female presenting with a steroid-resistant nephrotic syndrome. However, the search for WT1 intronic mutation is unlikely to be positive, unless the patient has a 46, XY karyotype, or a familial disease. In 46, XX patients, the genital development is normal; in 46, XY patients, the gonads are fibrous, not functional, and should be removed due to the high risk of gonadoblastomas [29].

Nail-Patella Syndrome

The nail-patella syndrome (NPS, also called osteo-onychodysplasia) is a rare autosomal dominant disorder linked to chromosome 9q34. NPS is characterized by bone and nail abnormalities. Renal involvement occurs in 40% of cases. NPS is caused by heterozygous loss of function mutations in LMX1B, a member of the LIM homeodomain protein family [30].

Absence, dysplasia, or hypoplasia of the nails is present at birth in 90% of patients. These abnormalities are bilateral and symmetrical and predominate on the fingernails, particularly the thumb and index fingers. The patella may be absent or hypoplastic, causing lateral slippage during knee flexion and sometimes knee pain or complications of effusion, arthritis or arthrosis. Elbow subluxation and limitation of forearm movement are not infrequent. X-rays reveal radial head and humeral hypoplasia. The pathognomonic radiologic finding of the disease is bilateral iliac horns arising from the anterosuperior iliac crest, observed in 50% of the patients.

Renal disease develops in half of the patients with the nail-patella syndrome, with considerable variation among families and also within single families. Symptoms are proteinuria (possibly nephrotic), hematuria, and hypertension. ESRD develops in approximately 30% of patients, at a mean age of 33 1 8 years. For unknown reasons, some superimposed renal diseases (anti-GBM antibody disease, necrotizing vasculitis, membranous or IgA nephropathy) have been frequently reported.

Light microscopy usually reveals basement membrane thickening and nonspecific focal and segmental glomerulosclerosis. Immunofluorescence microscopy is typically negative. Electron microscopy shows a pathognomonic lesion of the glomerular basement

membrane, consisting of clusters of cross-banded collagen fibrils within the lamina densa. There is no correlation between the severity of the ultrastructural lesions and the clinical manifestations. Not surprisingly, immunohistochemical studies have shown different renal fibrillar collagen expression.

There is no specific therapy for nail-patella syndrome. The lesions do not recur after renal transplantation, and patients do not develop anti-GBM antibodies.

Fabry Disease

Fabry disease is an X-linked lysosomal disorder, characterized by -galactosidase deficiency. Estimates of incidence range from 1 in 40,000 – 60,000 males.

The first symptom is generally acroparesthesia, which is often very painful in children and may be relieved by carbamazepine or diphenylhydantoin. Skin angiokeratoma, corneal deposits, and decreased sweating develop during adolescence in affected hemizygous males. Proteinuria appears between 10 and 25 years of age; progressive renal failure follows, usually reaching end-stage between 35 and 50 years. Patients are at risk of developing other cardiovascular complications, such as ischemic cerebrovascular and coronary accidents or atrioventricular block. All these manifestations, including kidney involvement, are due to glycolipid accumulation in lysosomes, predominantly of vascular cells. Fabry disease is largely under-recognized, and although symptoms in males start during childhood, most cases are not diagnosed until adulthood. Diagnostic clues are familial history, symptoms, measurement of -galactosidase activity in leukocytes, demonstration of typical inclusions on a tissue biopsy, and genetic analysis. Carrier (heterozygous) females occasionally have slight or moderate symptoms, because of random X-chromosomal inactivation. Corneal deposits are found in 80% of them. Gene testing allows identification of the carrier state, whereas biochemical enzyme measurements may be inconclusive in heterozygous females.

Kidney transplantation is an adequate treatment of ESRD in Fabry patients, and the disease does not generally recur. Enzyme replacement therapy using recombinant human -galactosidase is now available, safe, and reverses substrate storage in the lysosomes. The early results of clinical trials also suggest organ function improvement. All males with Fabry disease and all females with substantial disease manifestations should receive this treatment as early as possible [31].

Hereditary Nonlithiasic Renal Diseases with Tubular Involvement

Fanconi Syndrome

This syndrome is characterized by complex dysfunction of proximal tubules, i.e. low molecular weight proteinuria ($_2$-microglobulinuria), hypokalemia, defective transport of bicarbonate (type II renal tubular acidosis), glucose (glucosuria), amino acid (hyperaminoaciduria), urate (hypouricemia, uricosuria), phosphate (hypophosphatemia, hyperphosphaturia, rickets), and citrate (hypercitraturia); and polyuria. When hereditary, the Fanconi syndrome may be idiopathic (autosomal dominant) or secondary to various inherited metabolic diseases: cystinosis, type I glycogenosis, mitochondrial cytopathies, Lowe syndrome, Wilson's disease, galactosemia, tyrosinemia, and fructose intolerance. We will focus mainly on cystinosis, the most frequent cause in children.

Table 6. Main inherited tubular diseases (proximal tubule excepted).

Tubular segment disease	Transmission pattern	Age at onset/ discovery	Phenotype	Mechanism/ gene	Treatment
Bartter syndrome [34]	AR	childhood	hypokalemia, metabolic alkalosis, growth retardation, hypercalciuria, +/– nephrocalcinosis	NaCl reabsorption defect due to various mutations: type I: NKCC transporter, type II: ROMK channel, type III: CLCkb channel	symptomatic, indomethacin, COX-2 inhibitors, ACEI, angiotensin II blockers
Gitelman syndrome [35]	AR	childhood +/–, adulthood +++	hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria, +/– chondrocalcinosis	NaCl reabsorption defect (TSC sodium-chloride cotransport mutations)	symptomatic
Liddle syndrome [44]	AD	childhood ++, adulthood ++	hypertension, hypokalemia, low renin and aldosterone	increased absorption of Na (sodium channel, activating mutation of or subunits)	amiloride (+++), low-salt diet
Pseudohypoaldosteronism, type I [36]	AD, AR	newborn	dehydration, hyponatremia, hyperkalemia, high renin and aldosterone	decreased absorption of Na (sodium channel, inactivating mutations of or subunits)	NaCl
Gordon syndrome (Pseudohypoaldosteronism, type II) [45]	AD	neonates, children	hypertension, hyperkalemia, acidosis hypercalciuria, growth retardation, low renin and aldosterone	WNK4 kinase mutations, sodium and chloride hyperabsorption	thiazide diuretics

Table 6. Continuation

Tubular segment disease	Transmission pattern	Age at onset/ discovery	Phenotype	Mechanism/ gene	Treatment
Nephrogenic diabetes insipidus [46]	XR/AR	newborn	insipid polyuria, ADH resistance	ADH V2 receptor mutation (X-linked), aquaporin 2 mutation (RA)	hydration, thiazide, NSAIDs

AR: autosomal recessive, AD: autosomal dominant, ADH: antidiuretic hormone, NSAID: non-steroid anti-inflammatory drug.

Cystinosis is a metabolic lysosomal storage disease of cystine affecting most of the body cells and is characterized by both renal and extrarenal symptoms. Cystine is derived from protein degradation within the lysosome, then is normally transported through the lysosomal membrane to the cytosol, transformed into cysteine, and finally utilized. Cystinosis involves a defect in the transport system in which the poorly soluble cystine accumulates inside the lysosome and forms crystals. Cystinosis is transmitted as an autosomal recessive trait. The causative gene, CTNS, encodes cystinosin, a lysosomal membrane protein responsible for cystine transport [32].

Three forms of cystinosis have been described: the infantile form found in 1/100,000 to 1/200,000 children, the intermediate (also called adolescent or late-onset) form, and the adult (benign) form.

The first renal symptoms of infantile cystinosis appear before 6 months of age, with varied manifestations of the Fanconi syndrome. The tubular losses gradually decline after age 6, as renal failure progresses. ESRD is typically reached before 12 years of age. Cystine may also accumulate in other tissues both before and after kidney transplantation. Eye involvement consists of photophobia, then retinal depigmentation and visual impairment. Hypothyroidism, portal hypertension, hepatomegaly, splenomegaly, diabetes mellitus, muscle weakness, low testosterone levels, incomplete pubertal development, and central nervous system manifestations of encephalopathy, pyramidal signs and cranial nerve palsies may also occur. The diagnosis of cystinosis can be confirmed by determining the intraleukocytic cystine content. Prenatal diagnosis is available.

The administration of cysteamine should be started as soon as the diagnosis of cystinosis is confirmed. Cysteamine concentrates within the lysosome and forms cysteine and cysteine-cysteamine complexes that are able to leave the lysosome, thus reducing the intracellular cystine content. This treatment has no effect on preexisting fluid and electrolyte losses, but if started early may slow the rate of progression to renal failure, improve growth, and prevent most extrarenal complications. Unfortunately, poor compliance due to numerous side effects limits the benefits of cysteamine. Topical cysteamine prevents corneal crystal deposition and reduces photophobia [33].

Table 7. Clinical factors suggesting hereditary urolithiasis.

- Early onset of urolithiasis
- Bilateral and recurrent urolithiasis
- Associated nephrocalcinosis
- Tubular dysfunction (growth retardation, polyuria, acidosis, etc.)
- Extrarenal symptoms

Other Tubular Disorders

Other inherited tubular disorders caused by mutations in transports, channels, enzymes and receptors are presented in Table 6 [34, 35, 36, 44, 45, 46]. Most of them are diagnosed soon after birth or during childhood, and rapid recognition is essential to provide symptomatic treatment. Others, like Gitelman or Liddle syndrome, are usually diagnosed in adults [36].

Urolithiasis Secondary to Hereditary Diseases

Hereditary urolithiasis (Table 7) accounts for 10 – 40% of all causes of lithiasis in children and up to 15% in adults. The most frequent inborn disorders are cystinuria, distal tubular acidosis, and hyperoxaluria (Table 8) [37, 38, 39]. Stone formation is secondary to an increased urine concentration of substances promoting crystal formation, e.g. cystine, calcium, oxalate or phosphate. The best diagnostic tool is infrared spectrophotometry, which can identify stone composition. Routine and specific biochemical examinations will help confirm the diagnosis. In many cases, an efficient specific preventive treatment is often available. The long-term renal prognosis is related to both the primary disease and therapeutic compliance.

Malformation Syndromes with Renal Involvement

See Table 9 for list.

Congenital Abnormalities of the Kidney and Urinary Tract

For review, see Moffat [40].

Kidney

Anomalies of Number

Bilateral renal agenesis is frequently associated with ureter and bladder development failure, Potter facies, pulmonary hypoplasia, and single umbilical artery. This abnormality is incompatible with life, and infants are stillborn or die soon after birth.

Unilateral agenesis is detected by fetal ultrasound during pregnancy or incidentally during childhood or adulthood. Compensative hypertrophy of the single kidney maintains normal renal function, but the kidney frequently develops focal and segmental glomerulosclerosis. The ureter and hemitrigone are absent on the affected side in most cases, and other organ abnormalities are possible.

Supernumerary kidney is rare and is sometimes bilateral. Ureters may be joined or separated.

Table 8. Hereditary urolithiasis (main causes).

Disease	Trans-mission pattern	Age at onset	Phenotype	Diagnosis	Specific treatment
Cystinuria [37]	AR	childhood +++, adolescence ++, adulthood +/–	fuzzy gray, +/– radiopaque stones	urinalysis: hexagonal cystine crystals; cystine excretion elevated, stone analysis	alkalinization of the urine (pH 7 – 7.5), D-penicilla-mine, tiopronin
Hyperoxaluria, type I [38]	AR	childhood +++, adolescence ++, adulthood +/–	radiopaque calcium stones, nephrocalcinosis, +/– renal failure	oxalate elevated, glycolate elevated, stone or crystal analysis (type 1c, monohydrated calcium oxalate), liver biopsy	vitamin B_6, trans-plantation (kidney, liver, or both)
Renal tubular acidosis, distal (type 1) [39]	AR/AD	childhood	radiopaque calcium stones, nephrocalcinosis, deafness	acidosis (metabolic), hypokalemia, urinary pH > 5 – 5.2	potassium citrate (or potassium or sodium bicarbonate)
APRTase deficiency	AR	variable	radiotransparent stones, +/– renal failure	2,8-dihydro-adenine crystals (stone analysis misleading: uric), enzyme deficiency	allopurinol
Dent's disease (and related diseases) [47]	XR	variable	radiopaque calcium stones, nephrocalcinosis, hypercalciuria, Fanconi syndrome, rickets, renal failure (in men)	CLCN5 mutation	thiazide

Renal Hypoplasia

Renal hypoplasia is defined as congenitally small kidney(s) with normal nephrons. Renal function is normal in proportion to the mass of the kidney. When bilateral, hypoplasia leads to renal failure.

Dysplasia should not be confused with hypoplasia. In addition to small kidney(s), various microscopic abnormalities are found,

Table 9. Various malformation syndromes with renal involvement.

Syndrome	Mode of inheritance	Gene(s)	Extrarenal signs	Renal manifestations
Bardet-Biedl syndrome [32]	AR	4 gene loci (BBS 1 –4)	retinal degeneration, polydactyly, obesity and short stature, mental retardation, hypogonadism	hypertension, tubular dysfunction (diabetes insipidus, acidosis), abnormal calyces, communicating cysts, fetal lobulation, interstitial nephritis, glomerular scarring, renal failure
Bronchiaoto-renal syndrome [48]	AD	EYA1 (8q 13.3)	laterocervical fistulas or cysts, outer, middle and inner ear anomalies	hypoplasia, dysplasia, aplasia (uni- or bilateral), various collecting system anomalies
PAX2 gene mutations syndrome [49]	AD	PAX 2	optic nerve coloboma	renal hypoplasia, vesicoureteral reflux

AR: autosomal recessive, AD: autosomal dominant.

including primitive pelvis, ducts, ductules, tubules, glomeruli, cysts, cartilage deposits, and fibrosis. Urinary tract obstruction, infection, hypertension, and poor renal function are common.

In oligomeganephronia, both kidneys are small and have interstitial fibrosis and a reduced number of nephrons, but markedly enlarged glomeruli and tubules. Symptoms of polyuria, polydipsia, salt loss, metabolic acidosis, and growth retardation appear during childhood. Progressive renal failure is the rule, and ESRD is reached before 16 years of age in most cases.

In Ask-Upmark kidney, one kidney is small and shows a lobulated hypoplastic area with thyroid-like tubules and hyalinized glomeruli, supplied by a narrowed artery. Hypertension is the main symptom and may be cured by partial nephrectomy.

Ectopic Kidney

Pelvic kidney is the most frequent variety of ectopia. It results from failure to ascend and is usually associated with malrotation (anterior pelvis). Ptotic kidney can be excluded by demonstration of a short ureter or a pelvic origin of the renal blood supply. Thoracic location is extremely rare and results from excessive ascent of one kidney. In crossed ectopia, one kidney has crossed the

midline and sometimes joins the opposite kidney. Blood supply and ureteric course are variable; obstruction and infection are not rare.

Horseshoe Kidney

In this condition, the lower poles of both kidneys fuse across the midline. The connection or isthmus runs anterior to the aorta and vena cava. Fusion prevents normal rotation, resulting in anterior pelvis. Ureters emerge anteriorly and obstruction can occur, with stone formation or infection. No therapy is required for uncomplicated horseshoe kidney. In case of obstruction, pyeloplasty or division of the isthmus may be required

Urinary Tract Abnormalities

Ureteric Duplication

In complete typical duplication, one ureter from the upper pelvis is dilated and opens ectopically in the bladder below a normal ureter running from the lower pelvis. Reflux of both poles, obstruction, and infection are frequent. In these cases, surgical reimplantation of the ectopic ureter should be discussed before massive dilatation or serious renal damage occurs. In incomplete duplication, ureters join prior to entry into the bladder. Complications are rare.

Ureteric Ectopia

The ectopic orifice can be located in the urethra, bladder neck, or trigone in both genders; uterus, vestibule, cervix, or vagina in females; and prostatic urethra, seminal vesicles, ejaculatory ducts, or vas deferens in males. Incontinence, UTI, and vaginitis are the main symptoms leading to diagnosis.

Retrocaval Ureter

The right ureter passes posterior to the inferior vena cava. Compression between vena cava and lumbar spine can result in obstruction and hematuria or right-sided symptoms, such as pain, urolithiasis, and infection. First symptoms often appear during adulthood. Intravenous pyelography (IVP) demonstrates a medially displaced right ureter, with a large superior portion. CT scan confirms the abnormality. Treatment consists of resection and anastomosis of the ureter.

Ureterocele

Ureteroceles may be uni- or bilateral and consist of a cystic ballooning of the intramural portion of the ureter commonly associated with duplication, ectopia, ureteric dilatation, and reflux. The intravesical protrusion may cause obstruction, resulting in persistent UTI. As the ureter usually drains a poorly functioning kidney, IVP shows the ureterocele as a radiolucent area in the bladder. Cystoscopy shows ureterocele protrusion into the bladder [41].

Vesicoureteral Reflux and Reflux Nephropathy

See chapter I-13.

Megaureter

Any ureter > 5 – 7 mm is a megaureter. This term should not be used alone, because this condition can be primary (congenital vesicoureteric junction abnormality) or secondary (e.g. high urinary flow, bladder or bladder neck dysfunction, posterior urethral valves, prunebelly syndrome). Congenital megaureters deserve complete evaluation to determine whether they are associated with obstruction and/or reflux, and to determine whether the best treatment is medical surveillance or surgical ureteric reimplantation [42].

Exstrophy of the Bladder

The diagnosis is made at inspection. The anterior abdominal wall and the anterior wall of the bladder are missing. The posterior wall of the bladder is everted and fused to the remaining abdominal wall. Epispadias, rudimentary penis, cleft clitoris, and other extraurinary malformations are frequently associated. Permanent incontinence produces skin lesions; UTIs are frequent, and bladder malignancy is not rare. Surgical treatment is difficult and often disappointing. Multistep reconstruction or urinary diversion with the Bricker procedure is usually considered [40].

Posterior Urethral Valves

In this frequent condition (1 in 5,000 males), the normal ridges running below the verumontanum to the lateral urethral walls become hyperplastic and obstructive with posterior urethra dilatation. Bladder hypertrophy, ureteric dilatation, reflux, dysplasia, or renal failure sometimes occur. Severe forms are diagnosed prenatally in most cases. Milder cases are discovered later in children presenting with UTIs, dysuria, incontinence, growth retardation, or hypertension. Endoscopic resection of the valves is the best treatment, but should be preceded by urinary drainage and antimicrobial therapy [43].

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Urinary Tract Infection (UTI)

Claire Pomeroy and James R. Johnson

Urinary tract infections (UTI) are a major cause of morbidity, mortality, and increased health care costs [1 – 3]. They can cause a wide variety of clinical manifestations ranging from asymptomatic bacteriuria to simple cystitis to life-threatening illnesses including sepsis [4]. Recent approaches to UTI treatment have emphasized protocols for management without office visits and short-term antibiotic therapy in women with uncomplicated cystitis, as well as awareness of the impact of emergence of resistant bacteria. To achieve optimal efficacy while limiting costs and the potential for adverse drug effects, the health care provider must tailor therapy with consideration of host status, probable infecting organisms, resistance patterns in the local community, and currently recommended practice guidelines [2, 5, 6].

Asymptomatic Bacteriuria

Bacteriuria unaccompanied by UTI symptoms is present in 1 – 3% of young women but < 0.1% of young men. Increasing percentages of both men and women develop bacteriuria as they age. At least 10% of elderly men and 20% of elderly women have asymptomatic bacteriuria [7]. Bacteriuria is nearly universal in chronically catheterized patients. Under most circumstances, if the patient does not have symptoms of UTI such as dysuria or fever, bacteriuria should not be treated with antibiotics, regardless of the presence or absence of pyuria [2].

Nevertheless, asymptomatic bacteriuria does require treatment in some groups of patients. Specifically, it is important to treat children with asymptomatic bacteriuria to decrease the chances of renal damage and long-term renal insufficiency. Patients scheduled to undergo urinary tract instrumentation or surgery should also be screened, and if found to have asymptomatic bacteriuria, they should be treated with antibiotics to reduce the risk of procedure-induced urosepsis [2]. Up to 20% of pregnant women with asymptomatic bacteriuria may develop pyelonephritis. For this reason, routine screening of urine and treatment of asymptomatic bacteriuria are components of appropriate prenatal care [6, 8, 9]. Asymptomatic bacteriuria in these patient groups should be treated based on the results of susceptibility testing, usually with a 3-day course of trimethoprim-sulfamethoxazole (TMP-SMX), oral fluoroquinolones (avoid in pregnancy and children), amoxicillin, nitrofurantoin, or an oral cephalosporin. Some authors also recommend that other patients at particular risk for severe consequences of infection, such as neutropenic patients, should be treated with antibiotics if they develop asymptomatic bacteriuria.

Early observations associating asymptomatic bacteriuria with increased mortality in the elderly raised concerns that this condition

might contribute to mortality. However, it is now well substantiated that a causal connection cannot be established between asymptomatic bacteriuria and mortality in the elderly [7, 10]. Furthermore, treatment of such patients with antibiotics is quite ineffective in producing lasting urinary tract sterility. In fact, treatment of asymptomatic bacteriuria in the elderly has been shown to be associated with adverse medication effects, selection of resistant organisms, and possibly increased mortality [6].

Nonantibiotic approaches to the prevention of bacteriuria have been attempted, including use of estrogen replacement therapy for elderly women and cranberry juice consumption in the elderly. Oral or topical estrogen replacement therapy in postmenopausal women with recurrent UTI reduces the frequency of bacteriuria, possibly because of the effectiveness of such therapy in restoring a premenopausal vaginal microenvironment and diminishing vaginal colonization with coliform bacilli [11]. Daily consumption of cranberry juice for 6 months significantly decreased the prevalence of bacteriuria among elderly residents of a home for senior citizens [12]. However, most of the episodes of bacteriuria were asymptomatic, so the clinical value of the observed preventive effect could be questioned. Nonetheless, there were trends towards decreased antibiotic use and fewer symptomatic UTI episodes in the treatment group, suggesting that the intervention may have provided a meaningful benefit.

Symptomatic UTI

Symptomatic UTIs range from simple cystitis to pyelonephritis to invasive febrile UTI with bacteremia [3, 13]. UTIs may be further classified as uncomplicated or complicated by the presence of anatomic or functional abnormalities of the urinary tract or by underlying medical illnesses. In practice, it is often difficult to definitively classify patients into one of these categories. The important principles are that it is critical to treat all symptomatic UTIs and that the required intensity and duration of therapy increase in proportion to the severity of the clinical syndrome (Table 1) [3, 6]. The antimicrobial agent and duration of therapy should be selected based on the host status including presence of complicating conditions, the identity and susceptibility pattern of the pathogen (whether directly determined or extrapolated from aggregate statistics), and the agent's cost and potential side effects [13, 14]. Uncomplicated cystitis can usually be treated with a short course of antibiotics, whereas complicated or invasive UTIs often are more difficult to eradicate and require more aggressive antibiotic therapy, as well as evaluation and treatment of underlying urologic abnormalities or medical conditions [6].

Lower UTI – Cystitis

Epidemiology

Acute bacterial cystitis is a commonly encountered health problem, accounting for over 5 million visits to physician offices and over $1 billion in medical costs annually in the United States [2]. Uncomplicated cystitis is defined as an infection of the bladder, usu-

Table 1. Factors Suggestive of Increased Likelihood of Complicated or Invasive UTI

Demographics	Male sex, age < 18 or > 65 years, pregnancy
Symptoms	Duration of > 7 days Rigors, flank pain, fever > 101°F (38.3 °C), or other symptoms suggestive of pyelonephritis or bacteremia
Risk factors	Urinary catheterization or recent urologic surgery/instrumentation Obstruction or anatomic defects of urinary tract; functional defects (neurogenic bladder, reflux) Diabetes, sickle cell anemia, immunosuppression (steroids, chemotherapy, HIV infection) Renal insufficiency, polycystic kidney disease, renal transplantation Recent hospitalization or residence in nursing home
Past history	History of childhood UTI 4 ≥ UTIs in past year or pyelonephritis within past 3 months Failure of antibiotic treatment for UTI in past 1 – 3 months

ally bacterial, in an otherwise healthy young woman with normal urinary tract anatomy and renal function. Nearly one-half of women suffer an episode of cystitis during their lifetime. Risk factors for cystitis include female gender, sexual activity, history of previous UTI, use of spermicide-diaphragm contraception, postmenopausal state, and possibly being a nonsecretor of blood group substances [15]. Vaginal colonization with *Escherichia coli* (which normally is absent from the vagina) is promoted by sexual intercourse and the use of spermicide-diaphragm contraception [16]. Spermicides are more toxic to the normal lactobacillus-based premenopausal vaginal flora than to *E. coli*, facilitating overgrowth by *E. coli* [17]. Similar alterations in vaginal flora are also observed in postmenopausal women due to hypoestrogenism [11] and in patients receiving antibiotics, especially β-lactam agents [16]. Some studies indicate that women of the nonsecretor phenotype have a greater risk of recurrent UTI, a higher prevalence of vaginal colonization with gram-negative bacilli, and increased bacterial adherence to vaginal epithelial cells compared to secretor women, possibly because of the expression by nonsecretors' cells of unique receptor glycolipids for P-fimbriated *E. coli* that are not present in the cells of secretor women [3, 16, 18 – 20].

Pathogenesis and Pathology

The vast majority of bladder infections in women are due to ascent of pathogens from the rectum to the vagina and then into the urethra and bladder [3, 4]. In women with uncomplicated cystitis, infection is most commonly caused by *E. coli* (80%), *Staphylococcus saprophyticus* (10 – 15%), and only rarely by other gram-negative bacteria or other organisms [2, 17]. While complicated UTIs still are most often due to *E. coli* (about 50%), they are more likely than uncomplicated cystitis to

involve infection with other gram-negative bacteria including *Klebsiella, Proteus, Pseudomonas, Serratia,* or *Enterobacter*. In addition, *Enterococcus* may be detected, and *Candida* and other yeasts are encountered with increasing frequency. In general, bacteria must have substantial intrinsic virulence to overcome the normal host's urinary tract defenses and cause infection. In contrast, organisms of lesser intrinsic virulence can infect patients with impaired defenses. However, these infections due to less virulent organisms in compromised hosts may paradoxically be more difficult to treat [6].

Manifestations

The clinical syndrome of cystitis is defined by the presence of symptoms localized to the bladder and urethra including frequency, dysuria, and suprapubic pain, without concomitant evidence of renal or systemic involvement. Dysuria due to acute cystitis must be differentiated from that caused by other inflammatory or infectious conditions, including vaginitis, sexually transmitted diseases, and miscellaneous noninflammatory causes of urethral discomfort.

Diagnosis

Bacterial cystitis traditionally has been defined microbiologically by the presence of $\geq 10^5$ colony-forming (CFU) units of bacteria/mL of urine. However, it is now well recognized that UTIs with lower bacterial counts of $10^2 - 10^4$ CFU/mL are responsible for dysuria and frequency in many women [2]. Although a pretreatment urine culture allows for precise targeting of antimicrobial therapy based on the known urinary organisms and their susceptibility patterns, the predictability of the infecting pathogens in cystitis occurring in healthy young women allows such patients to be treated presumptively without a urine culture when the clinical presentation strongly suggests cystitis. Collection of a urine specimen for a quantitative culture before the institution of therapy for UTI is appropriate for patients with complicating factors and in whom pyelonephritis or bacteremia is suspected, and for those who have failed to respond or responded poorly to empiric therapy. Patients recently treated with antimicrobial agents should also usually have pretreatment urine cultures because they are at greater risk of infection with resistant organisms.

Management

Young women with presumed uncomplicated cystitis can often be managed successfully without a traditional physician office visit, e.g. over the telephone or through a clinic by a physician extender who follows a practice guideline. Patients should be screened for risk factors suggestive of a complicated UTI and for evidence of another condition causing the symptoms, especially sexually transmitted disease. If this evaluation is unremarkable, a presumptive diagnosis of uncomplicated cystitis can be made and an empiric trial of antibiotics recommended.

A variety of nonspecific therapies have been advocated for patients with uncomplicated cystitis [21]. Agents to lower the urinary pH, such as hippuric acid or cranberry juice, are usually not necessary and have not been well documented to be beneficial. As an adjunct to antimicrobial therapy for patients with severe dysuria, treatment with oral phenazopyridine (Pyridium) in doses of 200 mg PO TID can provide symptomatic relief.

Table 2. Treatment Options for Uncomplicated Cystitis

Therapy	Comments
Single Dose	
TMP-SMX 2 double-strength (DS) tabs PO	Single dose therapy less effective than 3-day regimen.
Trimethoprim 400 mg PO	Failure of single doses of fluoroquinolones for cystitis due
Ciprofloxacin 250 mg PO	to *S. saprophyticus* is reported.
(or other fluoroquinolones)	
Three-Day Regimens	
TMP-SMX 1 DS tab PO BID	3-day TMP-SMX regimen is a good strategy for most young women with uncomplicated cystitis.
Trimethoprim 100 mg PO BID	Trimethoprim useful in sulfa-intolerant patients.
Ciprofloxacin 250 mg PO BID	Fluoroquinolones useful for patients with complicated UTI
(or other fluoroquinolones)	or those who fail or who are intolerant of TMP-SMX.
Seven-Day Regimens	
As above but continued for 7 days	Indicated for men, diabetics, pregnant women (avoid fluoroquinolones), children (avoid fluoroquinolones), and the elderly, if symptoms present for 7 days, and for other complicated cystitis.

Antibiotic Choice

The choice of antimicrobial therapy for cystitis depends upon the resistance patterns in the local community as well as the underlying host status (Table 2). Knowledge of the antibiotic-resistant patterns in the community or institution, including in nursing homes, should be used to guide the choice of empiric antibiotic therapy while urine culture results.

TMP-SMX is considered by many experts to be the drug of first choice for uncomplicated cystitis because of the low cost and well-established efficacy. Adverse effects may be less frequent with TMP alone, which is a good choice in patients intolerant of sulfonamides. However, in some locales, resistance to TMP-SMX is increasingly prevalent among *E. coli* and other urinary tract pathogens. In these communities, fluoroquinolones may be the preferred agents for empiric therapy. These drugs' excellent spectrum of activity against gram-negative uropathogens and the infrequency of side effects are advantageous. However, the cost of these agents and concerns about the emergence of resistance have lead many to exclude them from consideration as first-line empiric therapy for uncomplicated cystitis. Because of a high prevalence of resistance among uropathogens and their inferior performance in clinical trials, oral first-generation cephalosporins or ampicillin are not generally considered to be first-line therapy for cystitis. However, in cases with confirmed sensitivity, these agents may be reasonable alternatives if TMP-SMX and fluoroquinolones are contraindicated.

Complicated cystitis can be treated initially with fluoroquinolones, which have emerged as drugs of choice in this setting because of their excellent activity against many gram-negative bacteria and their satisfactory per-

formance in clinical trials when compared with traditional intravenous regimens. Subsequent therapy should be guided by the results of urine culture and susceptibility patterns of the identified pathogen.

Duration of Therapy

It is now well recognized that "short course" therapy is adequate for treatment of most women with uncomplicated cystitis. An empiric 3-day course of TMP-SMX or an oral fluoroquinolone is the currently recommended treatment duration [6, 22]. Three-day treatment courses have been well demonstrated to cost less, have fewer side effects, and have comparable efficacy to traditional therapeutic approaches using 7 to 14 days of antibiotics. Single-dose therapy is the most convenient but is associated with higher failure rates than those observed with multiple dose regimens. Longer regimens such as the traditional 7-day regimen are very effective but produce more side effects and should be reserved for high-risk patients. Treatment for a minimum of 7 – 10 days is recommended for UTIs in men, even in the absence of signs of renal or systemic involvement, due to the increased likelihood of undetected underlying complicating factors and the paucity of studies of short-course (3-day) therapy of UTI in men. Men or women known to have complicated cystitis should be treated with a 7- to 14-day course of antibiotics, and even longer periods of therapy may be necessary in selected subgroups.

Prognosis

Complete recovery from cystitis is the norm. Post-therapy urine cultures have traditionally been recommended to confirm successful eradication of infections in patients with acute UTI. However, this is not often necessary in patients with uncomplicated cystitis [1]. In one study, the incidence of symptomatic UTI following therapy for acute cystitis was not reduced when routine follow-up cultures were used (as compared to performing cultures in symptomatic patients only). Post-therapy cultures need to be obtained in nonpregnant women only when there are persisting symptoms or known complicating factors. In contrast, for children, men, pregnant women, patients with obstructive uropathy, or patients with relapsing infection, a follow-up culture should be obtained as a "test of cure".

One challenge for the physician is determining the indications for urologic studies for patients with UTIs. Traditionally, it has been recommended that men with UTIs should be evaluated for predisposing anatomic abnormalities. However, it is now recognized that young men, especially homosexual men and heterosexual men whose female sex partners have vaginal colonization with uropathogens, may develop cystitis in the absence of abnormalities of the urinary tract. In older men, it is certainly still reasonable to screen for prostate abnormalities or neurogenic bladder. More studies are needed to clarify this issue.

Upper UTI – Pyelonephritis

Epidemiology

Pyelonephritis is infection of the renal pelvis and renal parenchyma. Acute bacterial pyelonephritis is one of the most common serious infections of adult women and can also affect children and adult men. In the United States, more than 100,000 patients are admitted to the hospital for an average of 6 – 7 days because of renal infection. The annual risk for hospitalization for pyelonephritis among adults has been estimated at 1 per 1000

women and 0.3 per 1000 men [23]. Many more patients are treated for pyelonephritis as outpatients [24 – 27]. The ratio of pyelonephritis to cystitis episodes has been estimated at approximately 1 : 20 [28]. Increased risk for pyelonephritis is predicted by many of the same factors as for cystitis. In addition, among children, P_1 blood group phenotype is associated with increased risk of pyelonephritis. Pyelonephritis is also more likely in patients with abnormalities of the urinary tract including neurogenic bladder, posterior urethral valves (in infant boys), congenital vesicoureteral reflux (in girls), chronic urinary catheterization, urolithiasis, and kidney transplantation [29 – 32].

Pathogenesis

In most cases, pyelonephritis arises as an ascending infection wherein bacteria enter the urinary tract via the urethra, establish bladder colonization, and then ascend up the ureters to the kidneys [3, 32]. Usually the pathogens are derived from the host's own intestinal, and in women, vaginal, flora [16, 33]. If the patient is catheterized, the urine can be contaminated from the hands of healthcare workers or other environmental sources [34].

The microbial flora of pyelonephritis is quite similar to that of acute cystitis, with *E. coli* accounting for over 80% of cases and other gram-negative bacilli including *Klebsiella* and *Proteus*, as well as *S. saprophyticus* and *Enterococcus* making up the remainder of cases [32]. The *E. coli* strains that cause pyelonephritis are quite distinct from ordinary intestinal *E. coli* and belong to a limited number of genetic lineages characterized by specific antigens and other properties that promote invasion and inflammation within the upper urinary tract [32, 35]. *E. coli* strains that cause pyelonephritis are likely to express adhesins including P fimbriae, which recognize Gal (α1-4) Gal-containing receptors on host epithelial surfaces via their adhesion molecule, PapG. PapG occurs in 3 known variants. Class II variants are the most common among *E. coli* strains that cause pyelonephritis and bacteremic UTIs, whereas class III variants predominate in cystitis. Other virulence factors of *E. coli* include the cytotoxin alpha hemolysin, the aerobactin iron sequestration system, polysaccharide capsules, lipopolysaccharide, and serum resistance proteins [19, 35].

Host factors also can promote ascending infection. Ascent of bacteria up the ureters is more common in patients with vesicoureteral reflux, whether due to underlying congenital or acquired urological abnormalities or secondary to acute changes in ureteral peristalsis induced by irritation of the ureter by lipopolysaccharide from adherent bacteria [32]. Pathogens can move from the renal pelvis into the collecting ducts and tubules due to intrarenal reflux [32]. Pyelonephritis is promoted during pregnancy by physiologic urethral hypotonia and partial ureteral obstruction.

Pathology

Pathogenic bacteria in the urinary tract adhere to the mucosa and trigger inflammation with production of proinflammatory cytokines and influx of polymorphonuclear leukocytes and other inflammatory cells [20]. Reactive oxygen species, leukotrienes, and prostaglandins act in concert with bacterial cytotoxins to produce tissue damage and renal vasoconstriction [19, 32]. The kidney becomes edematous and infiltrated with leukocytes, tubules may become necrotic, and microscopic and macroscopic abscesses may form.

Clinical Manifestations

Patients with pyelonephritis typically present with progressive flank pain, malaise, fevers, and possibly gastrointestinal symptoms of nausea and vomiting. These symptoms of pyelonephritis may be preceded or accompanied by symptoms of acute cystitis such as dysuria, urinary frequency, and urgency. On physical examination, patients are generally more ill appearing than those with simple cystitis. They are febrile and often are dehydrated and tachycardic. Tenderness over the costovertebral angles can be elicited with palpation or percussion. However, atypical presentation of pyelonephritis is not uncommon [36]. Symptoms may localize to the abdomen, pelvis, or back. Patients with sensory impairment may have minimal local symptoms and present solely with fever or hypotension.

Diagnosis

The clinical diagnosis of pyelonephritis is based on characteristic symptoms and signs and supportive laboratory tests [37]. Urinalysis and urine culture with susceptibility testing should be obtained in all patients with suspected pyelonephritis [2]. A gram stain of the urine is particularly helpful in confirming the presence of bacteria and suggesting a likely bacterial type, distinguishing between gram-positive and gram-negative pathogens. In the absence of prior antimicrobial therapy, the urine culture in most patients with pyelonephritis will have $> 10^5$ CFU of bacteria/mL of urine. Antimicrobial sensitivity testing is important and should be used to tailor antibiotic choices when the results are available. Blood cultures will be positive in a large percentage of patients with acute pyelonephritis. Their use in uncomplicated pyelonephritis is considered optional by some experts because bacteremia is usually adequately treated with the antibiotics chosen for the UTI, and clinical outcome is most often independent of blood culture results.

Imaging studies are not routinely needed for the diagnosis or management of acute pyelonephritis [30, 37, 38]. However, in patients who fail to respond appropriately to therapy, further diagnostic studies and interventions are indicated [38]. Suspicion of obstruction or renal abscess should prompt additional evaluation. If obstruction is suspected, abdominal roentgenograms to screen for urinary calculi may be appropriate, followed by excretory urography if indicated. Computed tomography (CT) scanning may provide the best definition of anatomical abnormalities [39]. Contrast-enhanced CT scan facilitates detection of abscesses and allows their differentiation from surrounding inflamed tissue. Streaky or wedge-shaped hypodense areas that fail to concentrate contrast material normally are indicative of pyelonephritis. Other CT findings in pyelonephritis may include a swollen, enlarged kidney, focal bulges of the kidney, and inflammatory stranding in the perinephric fat. Under the new terminology, these CT findings are now labeled as “acute pyelonephritis” by the radiologist, and modifiers are used to describe the specific observed anatomic abnormalities [40]. The extent and severity of the CT findings have been demonstrated to correlate with risk of bacteremia and other complications, including death. Ultrasound is now recognized as less sensitive than CT for detecting or following pyelonephritis but remains useful for detecting perinephric abscesses or obstruction and hydronephrosis. Single photon emission CT (SPECT) scanning using Tc-99m (dimercaptosuccinic) acid (DMSA) is even more sensitive than CT for detecting inflammation but is less useful in differentiating abscesses from inflamed tis-

Table 3. Treatment Options for Pyelonephritis

Entity	Drug	Duration
Subclinical or mild-moderate pyelonephritis (outpatient)	TMP-SMX 1 DS tab PO BID Ciprofloxacin 500 mg PO BID (or other fluoroquinolones)	14 days
Moderate-severe pyelonephritis (inpatient initially)	*Enterococcus:* IV ampicillin ± gentamicin; Gram-negative bacteria: IV fluoroquinolone, third-generation cephalosporin, aztreonam or gentamicin	IV therapy until clinically stable, then complete 14-day course with oral antibiotics
Complicated pyelonephritis	IV broad spectrum antibiotics, usually to include agents active against *Pseudomonas*, especially if nosocomial or nursing home-acquired infection	IV therapy until stable, followed by oral drugs to complete a minimum of 14 days; longer therapy may be necessary.

sues. Nonenhanced spiral CT may be superior to conventional CT or excretory urography for detecting urolithiasis.

Clinical Management

Severity of illness is the main determinant of the need for hospital admission and parenteral therapy in the patient with pyelonephritis [23, 26, 27]. If a reliable patient is clinically stable and able to take oral medications, a trial of outpatient therapy can be considered and can result in significant cost savings [25]. Parenteral therapy is needed for the patient with nausea and vomiting who is unable to take oral medications. If such a patient is otherwise stable, home intravenous (IV) antibiotic therapy may be an option. For the more seriously ill patient, especially if fever, rigors, or unstable blood pressure suggest sepsis syndrome, hospitalization is required. Acute pyelonephritis in the pregnant woman requires hospitalization because of the high risk of bacteremia and potential for significant morbidity and mortality for both mother and baby [23, 41, 42].

Antibiotic Choice

Antibiotic choices for the treatment of pyelonephritis depend upon the severity of symptoms, the causative organisms, and the presence or absence of complicating factors [37, 43] (Table 3). For mild cases of pyelonephritis, outpatient therapy with oral antibiotics such as TMP-SMX or fluoroquinolones in the same doses prescribed for cystitis but continued for 2 weeks may be sufficient. If hospitalization and parenteral therapy are required, options for treatment of uncomplicated pyelonephritis include IV, fluoroquinolones, aminoglycosides, or third-generation cephalosporin drugs (Table 3). If the in-

itial gram stain of the urine culture suggests the possibility of *Enterococcus*, IV ampicillin with or without gentamicin should be considered. Other possible agents include imipenem or other broad-spectrum antibiotics. The choice of antibiotics should be adjusted as indicated by the infecting organism's susceptibility pattern, when available. For hospitalized patients, parenteral antibiotics should be continued until the patient is stable, after which oral antibiotics can usually be used to complete the treatment [6, 43, 44].

Care must be exercised in the choice of antibiotics for pregnant women [6, 45]. Fluoroquinolones should be avoided in pregnant women (and in children) because of concerns about their effect on cartilage development. Aminoglycosides should be used with caution due to the possibility of fetal cranial nerve VIII damage, and TMP-SMX should be avoided near term to avoid kernicterus in the baby. Tetracyclines are contraindicated in children and pregnant women.

Duration of Therapy

The optimal duration of therapy for pyelonephritis has not been well studied. Although treatment for as long as 6 weeks has traditionally been advocated, > 2 weeks of treatment is usually not necessary for uncomplicated cases [46, 47]. Some studies have explored the possibility of reducing the duration of therapy to ≤ 1 week [30, 44], but concern remains that there may be an increased risk of relapse with such a short course of treatment [43]. Fortunately, the availability of oral fluoroquinolones increases the ease of IV to PO switching and again allows earlier discharge from the hospital. Therapy for > 14 days may be necessary in selected cases of complicated pyelonephritis or in men if prostatic infection is suspected.

Prognosis

With appropriate antimicrobial therapy, the prognosis for patients with pyelonephritis is complete recovery. In patients who fail to respond clinically after 72 hours of therapy with appropriate antibiotics, additional evaluation is indicated. Careful review of antibiotic sensitivity based on culture results should be undertaken [48]. Radiographic imaging to rule out obstruction, anatomic abnormalities, or intrarenal or perinephric abscesses can be considered [38]. Renal ultrasound, CT scans and possibly an intravenous pyelogram (IVP) may be necessary to detect abnormalities requiring surgical intervention.

Careful follow-up of patients with pyelonephritis is important, but the specifics of the required evaluation are unclear. At the least, instructions to return if symptoms recur is critical. The role of follow-up office visits, urinalysis, or urine culture is undefined. Follow-up "test of cure" urine cultures should be done within 1 – 2 weeks of completion of therapy in pregnant women, children, and patients with multiple episodes of pyelonephritis, and should be considered for other patients [49].

Complications

The intense renal inflammation associated with pyelonephritis can have functional consequences. Inflammation-induced tubular dysfunction can result in delayed excretion of contrast dyes and, rarely, overt acute renal failure (ARF) [36]. However, these changes usually are not clinically significant or persisting. Pyelonephritis can be complicated by bacteremia, especially during pregnancy and in older patients or those with obstructed urine flow. Septic shock with disseminated in-

travascular coagulation (DIC), adult respiratory distress syndrome (ARDS), and multiorgan failure can occur [43].

Particularly in hyperglycemic diabetic patients, rapid fermentation of glucose by the bacteria can produce gas within the kidney, causing emphysematous pyelonephritis (if the renal parenchyma is involved), gas abscess, or emphysematous pyelitis (if the renal pelvis or collecting system is involved) [50]. Papillary necrosis can also complicate pyelonephritis, especially among diabetics. In this circumstance, infection causes sloughing of the tissue, which can cause obstruction and worsen infection.

Kidney-associated abscesses may be intrarenal or perinephric [51, 52]. They occur predominantly in compromised hosts, especially in patients with diabetes, recent surgery or instrumentation of the urinary tract, or urinary reflux or obstruction. Those abscesses that develop as a complication of pyelonephritis are usually due to a gram-negative bacteria, especially *Enterobacteriacae*. In contrast, staphylococcal abscesses may occur secondary to bacteremia. Indeed, the isolation of *Staphylococcus aureus* in the urine in a febrile patient without urinary tract instrumentation signals the need for investigation of possible associated bacteremia. *S. aureus* abscesses should be treated with antistaphylococcal penicillin drugs or first-generation cephalosporins, whereas abscesses due to gram-negative bacteria should be treated with agents active against these organisms [51, 53]. Small abscesses may respond to medical management, but especially with larger abscesses, surgical or image guided needle drainage may be necessary [54, 55].

Recurrent UTIs

Recurrent infections pose important challenges to the patient's physician [1, 2, 18, 28, 56]. Differentiation between reinfection and relapse is critical to the correct management of these 2 very different conditions [2]. Reinfection implies newly-introduced infection with a new organism. Although such repeat infections are usually due to *E. coli*, the new organisms are different strains of this species. Risk factors for reinfection include sexual intercourse and use of diaphragm/spermicide as contraception [15, 56]. In contrast, relapse implies recurrent infection caused by the same organism, usually beginning soon after completion of an initial course of therapy, and is attributable to incomplete treatment of the initial episode. Relapse is more likely to occur in complicated UTI and is attributable to a persistent nidus of infection. Functional or anatomic abnormalities, prostatitis, or infected stones should be suspected.

Prevention of reinfection is focused on preventing reintroduction of bacteria into the urinary tract (Table 4). Oral antimicrobial therapeutic regimes have been shown to decrease the likelihood of reinfection and recurrent UTI [1, 2, 6]. For reliable patients, patient-initiated antibiotic therapy immediately after the onset of symptoms can be useful. In women who can accurately identify when they are developing a recurrence, a supply of antibiotics, usually TMP-SMX or a fluoroquinolone kept at home and initiated with onset of symptoms, can be effective. If recurrent UTI episodes are related to sexual intercourse, postcoital antibiotic prophylaxis can be helpful [57]. Because diaphragm/spermicide contraception is associated with high risk of urinary tract infection, alternative contraceptive methods should be considered. Continuous

Table 4. Management of Recurrent Cystitis Due to Reinfection

Post-coital prophylaxis	TMP-SMX 1 single-strength or 1 DS tab PO or Nitrofurantoin 50 – 100 mg PO
Continuous prophylaxis (daily or 3 times per week)	TMP-SMX 1 single-strength tab PO or Trimethoprim 100 mg PO or Nitrofurantoin 50 – 100 mg PO
Patient-initiated therapy	As recommended for single dose or 3-day therapy of cystitis

antibiotic prophylaxis can be used in patients with frequent (> 2 – 3 per year) episodes of UTI. Chronic prophylaxis (daily or thrice weekly) with low doses of TMP-SMX or a fluoroquinolone has been demonstrated to reduce the frequency of recurrences from 2 – 3 episodes per year to about 0.2 episodes per year among women with frequent UTI. Such prophylaxis is often continued for 6 months to a year and then interrupted to see if episodes of UTI recur. If so, prophylaxis can be resumed. Fortunately, emergence of resistant strains has not been a significant problem for women using long-term antibiotic prophylaxis for UTI. Finally, postmenopausal women with recurrent UTI may benefit from topical vaginal estrogen replacement therapy [11].

In contrast to reinfection, relapse of UTIs requires investigation of the underlying cause. A urine culture should be obtained and a full 7- to 14-day course of appropriate antibiotics initiated. Diagnostic studies should be considered to search for an occult source of infection in the kidney, perinephric space, or prostate and for urologic abnormalities including anatomic defects [18]. Renal, urethral, or bladder stones and other causes of obstruction need to be ruled out. Urinary tract stones may occur in patients with chronic infection due to a urease-producing organism such as *Proteus mirabilis*. Removal of calculi via lithotripsy or surgery is often necessary before antibiotics can effectively eradicate infection in patients with urolithiasis.

Catheter-associated UTI

Bacteriuria in patients with indwelling catheters occurs at a rate of 3 – 10% per day of catheterization and is nearly universal in patients with prolonged catheter use [58]. Routine treatment of asymptomatic bacteriuria in catheterized patients does not improve survival and often results in the selection of increasingly resistant microbes. Nevertheless, some bacteriuric patients will go on to develop symptomatic cystitis, pyelonephritis, and even bacteremia. Antibiotic therapy should be reserved for catheterized patients with significant symptoms or signs attributable to UTI [34].

Treatment of symptomatic UTI in the catheterized patient should include attempts to remove the catheter plus administration of appropriate antibiotics. Because catheterized patients often have infections due to bacteria other than *E. coli*, urine cultures are desirable to define the pathogen's identity and sensitivity patterns. Urine samples should be obtained directly from the Foley catheter and not from the drainage bag. Choice of initial empiric treatment should be based on review of the

organisms known to have previously infected the patient and on resistance patterns in the hospital or nursing home. TMP-SMX or fluoroquinolones are often reasonable choices until culture and sensitivity results are available, at which time therapy should be modified as needed. By definition, catheter-related infections are complicated UTIs, and antibiotics should be continued for ≥ 7 days.

Prevention of UTIs in catheterized patients is desirable but difficult [2]. The best preventive method is to avoid unnecessary use of urinary catheters. Use of diapers or pads, external drainage devices, or possibly intermittent catheterization is preferable to chronic catheterization [59]. Clean technique, as opposed to sterile technique, has been shown to be adequate for patients trained in self-administered intermittent catheterization [58]. Antibiotic prophylaxis may be useful for the patient with short-term catheterization [6], but this remains controversial. However, routine antimicrobial prophylaxis should not be used for chronically catheterized patients [2, 60]. This approach serves only to select antibiotic-resistant organisms [58, 60]. If chronic indwelling catheters must be used, meticulous handwashing by all caregivers should be emphasized. The role of local antibiotics and antibiotic impregnated catheters remains incompletely defined [2, 6, 61]. Reflux of urine from the collecting system into the bladder and breaks in the drainage system must be avoided.

The patient with neurogenic bladder and recurrent UTIs poses a particular challenge [62]. Intermittent catheterization or, in men, condom drainage with or without sphincterotomy can be useful. The use of alpha-blockers to control autonomic dysreflexia or of anticholinergic agents to improve incontinence should be considered. Transurethral sphincterotomy and external drainage may be needed to maintain low voiding pressures. Diversion procedures are required for some patients but are becoming less popular because of a variety of complications [62].

UTI in Children

In children, both asymptomatic bacteriuria and symptomatic UTIs should be treated with antibiotics, with drug choice determined by the results of urine culture [29, 31, 63]. Low bacterial counts in urine cultures from infants may reflect infection requiring treatment [64]. Short-course therapy is not appropriate, and antibiotics should be continued for 7 – 14 days. TMP-SMX is often appropriate as empiric therapy, and the acutely ill child with suspected pyelonephritis should receive treatment with parenteral antibiotics pending culture results [65]. Cure should be documented by follow-up urine cultures [29].

In many children, especially infants, UTIs should prompt diagnostic imaging because of the likelihood of discovering anatomic or functional urinary tract abnormalities and the high risk of renal damage from infection [18, 29, 30, 66, 67]. Ultrasonography is a commonly used initial test. A voiding cystourethrogram (VCUG) can be used to look for evidence of reflux in young children and in children with an abnormal ultrasound or a history suggestive of voiding dysfunction [30, 66]. Children found to have reflux should be placed on suppressive antibiotics at least until 5 years of age and have regular urine evaluations for unexplained febrile illnesses, with aggressive treatment of identified UTIs [31]. Surgical interventions are clearly required for obstructive lesions and may be considered in the child with reflux who develops recurrent UTI despite antibiotic therapy [66].

UTI after Renal Transplantation

Renal transplant recipients are at high risk for renal infection, both for mechanical reasons and because of the immunosuppressive therapy used to prevent graft rejection. Continuous prophylactic antibiotic therapy with TMP-SMX is commonly used in this context. Such therapy additionally provides protection against opportunistic infections such as nocardiosis, toxoplasmosis, or *Pneumocystis carinii* pneumonia, for which these patients are at risk. The efficacy of continuous TMP-SMX prophylaxis in preventing UTI and bacteremia in kidney transplant recipients was documented in a recent trial using both a standard dose (160 – 400 mg daily) and a higher dose regimen (320 – 800 mg daily). Emergence of resistance was not observed [6].

Prostatitis

Prostatitis syndromes can be divided into 4 types: acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostadynia [68, 69]. The diagnostic approach and therapeutic management differs markedly between these 4 conditions [70].

Acute bacterial prostatitis denotes bacterial infection of the prostate and usually manifests with an abrupt onset of symptoms [68]. The patient classically presents with fevers, dysuria, frequency, obstructive voiding symptoms, and extreme perineal pain. The diagnosis of acute bacterial prostatitis is often quite obvious, with extreme tenderness to palpation of the prostate. Indeed, vigorous prostatic massage should not be performed in these patients because of the risk of precipitating bacteremia. To confirm the diagnosis and an etiologic agent of acute prostatitis, a urinalysis and urine culture should be performed. The urine specimen will usually show significant pyuria and may reveal hematuria. Urine culture will be positive. The most common organisms identified are *E. coli* and less frequently *Enterococcus* and other gram-negative bacilli, including *Pseudomonas*.

Treatment of acute bacterial prostatitis consists of empiric antibiotic therapy followed by tailoring of this therapy based on the results of urine culture and sensitivity patterns. Currently, the drug of choice is considered by many to be a fluoroquinolone, but TMP-SMX is also a reasonable choice. If the patient appears seriously ill with a high fever and the possibility of bacteremia is suspected, hospitalization for treatment with broad-spectrum IV antibiotics and supportive care may be needed. On occasion, prostatic edema can be so severe that acute urinary retention can result. In this case, urologic consultation and treatment with suprapubic urinary drainage catheter is needed. When the patient has been stabilized, antibiotic therapy can be given orally. Acute bacterial prostatitis requires prolonged therapy with oral antibiotics. A minimum treatment duration of 30 days, and sometimes 6 weeks to 3 months, may be required.

Chronic bacterial prostatitis is characterized by relapsing urinary tract symptoms and evidence of prostatic infection [68]. The patient may have prostatic, perineal, or suprapubic discomfort, but the symptoms are usually more intermittent and milder than those observed in acute bacterial prostatitis. Prostatic massage may yield secretions that contain > 10 white blood cells per high power field. The presence of white blood cells in the expressed prostatic secretions but not in the pre-massage urine favors the diagnosis of

chronic bacterial prostatitis rather than recurrent cystitis. Most patients with chronic bacterial prostatitis have infection with a gram-negative bacillus, and the recurrent episodes are caused by the same organism. Treatment involves identification of the infecting organism and long-term (1 – 3 months) oral antibiotic therapy with agents such as TMP-SMX or fluoroquinolones. Some patients with chronic bacterial prostatitis may have prostatic calculi that harbor organisms capable of causing recurrent symptomatic episodes. These patients are particularly likely to require long-term antibiotic treatment to eradicate the infecting organism. Occasionally, transurethral resection of the prostatic gland (TURP) to remove prostatic calculi may be necessary.

Nonbacterial prostatitis is infectious prostatitis for which no identifiable bacterial etiology can be found [71]. Prostatic inflammation is evidenced by the presence of > 10 white blood cells per high power field in expressed prostatic secretions. However, in contrast to bacterial prostatitis, routine cultures of expressed prostatic secretions will be negative. Patients present with symptoms including prostatic, perineal, or suprapubic pain that may be indistinguishable from symptoms of chronic bacterial prostatitis. A variety of organisms have been postulated as possible etiologic agents of nonbacterial prostatitis, including *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma*, and *Trichomonas vaginalis* [72]. However, a definite role for any of these agents has not been established [71]. Nevertheless, many experts will give a trial of antibiotic therapy directed towards these unusual organisms in patients who present with nonbacterial prostatitis. Most commonly, a 2- to 4-week trial of doxycycline or tetracycline is attempted. If the patient experiences symptomatic improvement, it is possible that the antibiotic has treated an infecting organism. However, it may be difficult to distinguish between a placebo effect, coincidental improvement, nonspecific anti-inflammatory actions, and true response to the antibiotic. A variety of non-antimicrobial approaches have also been utilized in the treatment of nonbacterial prostatitis. The use of nonsteroidal anti-inflammatory agents, sitz baths, and avoidance of caffeine or alcohol, which can cause bladder irritation, have been advocated. Some patients may respond to treatment with alpha adrenergic blocking agents such as terazocin.

Prostadynia is a condition that can be quite distressing to the patient and difficult to treat [73]. Patients with prostadynia have symptoms similar to prostatitis but no evidence of infection or inflammation upon examination of urine or expressed prostatic secretions. The etiology of prostadynia is unknown. The role that stress or emotional problems play in the etiology of prostadynia remains to be defined. In some patients, urologic evaluation may reveal obstructive voiding physiology, but the vast majority of these patients will have no abnormalities on urological evaluation. Some patients with prostadynia may benefit from treatment with alpha adrenergic blocking agents [74] or muscle relaxants such as diazepam. Stress reduction and attention to underlying emotional problems contribute to the complete care of the patient [75].

Unusual Infections

Candida UTI

Candida UTI now represents the fourth most common cause of nosocomial UTIs (Table 5). The vast majority of candiduria epi-

Table 5. Treatment Options for Candidal UTI

Therapy	Comments
None	Appropriate in most asymptomatic patients without evidence of dissemination.
Fluconazole	Drug of choice for uncomplicated symptomatic cystitis (200 mg PO q day x 7) or ascending pyelonephritis (400 mg PO or IV q day).
Amphotericin B bladder washes (50 mg/L sterile water administered via triple-lumen catheter for 7 – 14 days)	Alternative for use in symptomatic patient requiring chronic Foley catheterization. No advantage over fluconazole in absence of fluconazole resistance.
Parenteral amphotericin B	Remains the drug of choice for disseminated disease in the immuno-compromised patient, but increasing evidence for efficacy of azole drugs.

sodes originate from the lower urinary tract. *Candida* UTIs may manifest as asymptomatic candiduria, cystitis, pyelonephritis, hematogenous renal candidiasis, or fungus balls [76]. When yeast is identified on urine culture, it is often advisable to determine that it is persistent. If a repeat urine specimen confirms the presence of yeast, it is important to consider the possibility of an underlying cause such as catheterization, prolonged antibiotic therapy, immunocompromising medical conditions, or urinary tract anatomic abnormalities.

If the patient with candiduria is asymptomatic, therapy is rarely appropriate. In the patient with a Foley catheter, it is reasonable to attempt at least one trial of changing or removing the catheter. Asymptomatic candiduria is widely overtreated, and treatment of asymptomatic infection is probably only justified before urologic surgery or manipulation and in the patient at high risk for disseminated fungemia such as the neutropenic host or other immunocompromised individual.

Symptomatic *Candida* cystitis usually should be treated with oral azoles [77]. Local bladder irrigation with amphotericin B is an alternative, particularly in the chronically catheterized patient. Ascending candidal pyelonephritis is an uncommon complication of candidal cystitis and usually only occurs in patients with diabetes and/or urinary obstruction. Instead, renal candidiasis is usually due to hematogenous seeding as a manifestation of disseminated fungal infection. Systemic therapy with fluconazole or amphortericin B is required for renal *Candida* infection irrespective of the route of acquisition. Patients with possible disseminated disease may need additional diagnostic or therapeutic interventions, plus a longer duration of treatment.

Viral UTI

In immunocompetent hosts, viral infections usually do not produce symptoms in the uri-

nary tract. However, in immunocompromised patients, significant manifestations such as hematuria, dysuria, and frequency can be associated with viral UTIs. Viral UTIs have been described as acute illnesses including acute hemorrhagic cystitis in children with adenovirus and in bone marrow transplant patients infected with adenovirus or polyoma virus. Viral UTIs can also occur as part of disseminated viral illnesses such as mumps, cytomegalovirus, measles, or varicella virus.

Tuberculous UTI

Tuberculous involvement of the urinary tract is well described. The pathogenesis of genitourinary tuberculosis (TB) is usually thought to involve hematogenous seeding of the renal cortex with progression to the medulla. Patients with renal TB are often asymptomatic but may present with dysuria or hematuria or, less commonly, with constitutional manifestations of disseminated tuberculosis. Evidence of active TB outside of the genitourinary tract is identified in < 10% of patients with renal TB, but evidence of old pulmonary infection can be found in most patients. Patients with genitourinary TB are often identified when "sterile pyuria", i.e. pyuria with negative routine bacterial cultures, is noted. *Mycobacterium tuberculosis* can be grown from the urine in the majority of cases. Genitourinary TB can be complicated by the development of ureteral strictures, hydronephrosis, and renal parenchymal abscesses. The IVP may demonstrate strictures or a beading pattern in the ureters, and ultrasonography may reveal hydronephrosis or an infiltrative process in the renal parenchyma. Treatment of renal TB is the same as that for other forms of TB.

Non-candidal Fungal UTI

Infection of the urinary tract with a variety of fungi, including cryptococcus, blastomycosis, or histoplasmosis, has been described. Treatment with the new azole drugs may be effective, but amphotericin-B therapy is sometimes necessary.

Parasitic UTI

A variety of parasites can also infect the urinary tract including *Schistosoma haematobium, Schistosoma mansoni*, or *Onchocerca volvulus*. Hematuria is suggestive of infection with *S. haematobium*, and the eggs of this trematode, as well the eggs of *S. mansoni*, can be detected in urine samples. Therapy of parasitic infections should be tailored to the specific organism.

The Dysuric Patient

Many conditions may cause the patient to present with dysuria [2]. About one-half of young women with dysuria will have classical bacterial cystitis with > 10^5 CFU of bacteria/mL urine on culture. In the remaining patients who have what has been termed "urethral syndrome", symptoms are due either to bacterial cystourethritis with fewer organisms or to other conditions. Bacterial cystitis must be distinguished from sexually transmitted diseases, vaginitis, and noninfectious etiologies of dysuria. Urethritis may be caused by genital *Herpes simplex* virus, *Chlamydia trachomatis*, gonorrhea, or other sexually transmitted diseases. *Candida* or *Trichimonas* vaginitis often presents with dysuria. Patients with *C. trachomatis*, gonorrhea, *Candida*, or

Trichimonas will respond to appropriate antimicrobial therapy for these conditions. Hypoestrogenism, urethral spasm, or chemical irritation can produce dysuria in the absence of infection. Finally, approximately 10% of patients with dysuria-frequency syndrome have no evidence of infection or any other identifiable cause for their symptoms.

Summary

Optimal management of acute UTI requires delineation of the patient's clinical syndrome and consideration of the underlying host status followed by selection of an antimicrobial agent and duration of therapy appropriate to the clinical situation. The choice of antimicrobial agent should be guided by the susceptibility pattern of the infecting organism and relevant characteristics of the antimicrobial agent, including efficacy, cost, pharmacokinetic properties and adverse effect profile. For women with uncomplicated cystitis, short-course therapy with 3 days of TMP-SMX or a fluoroquinolone is optimal. In other clinical situations, including complicated cystitis, pyelonephritis, prostatitis or bacteremic UTIs, longer courses of therapy are indicated. Pretreatment urine cultures are not necessary in most young women with uncomplicated cystitis but should be used to guide therapy in most other circumstances. Asymptomatic bacteriuria requires treatment only in children, pregnant women, and patients undergoing urinary tract instrumentation likely to be associated with bacteremia. Urologic investigation is warranted in patients not responding to therapy for UTI, when obstruction is suspected, with relapse of infection due to the same strain of bacteria and in children with symptomatic UTI, but not in the vast majority of women with uncomplicated UTI. Unusual organisms may cause UTI and should be considered based on historical or other clinical clues.

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Reflux Nephropathy

Billy S. Arant, Jr.

Introduction

The frequent association between chronic atrophic pyelonephritis and vesicoureteral reflux (VUR) was noted just over 25 years ago, and the term reflux nephropathy (RN) was quickly substituted for other words used previously to describe the localized injury and scarring from suppurative inflammation in the renal parenchyma [8]. In the pre-antibiotic era, chronic atrophic pyelonephritis was recognized as a common cause of hypertension and chronic renal insufficiency. In fact, up to 20% of patients at autopsy were found to have pyelonephritis and, when data were available, 45% of them were known to be hypertensive before death [43].

In 1929, an unusual but consistent pathologic finding was observed in kidneys of several patients with severe hypertension [6]. An aglomerular, fibrous band of tissue overlying a calyx gave the appearance of a circumferential groove in the renal parenchyma. These peculiar lesions were considered congenital and, subsequently, were referred to as the Ask-Upmark kidney [33]. Whether the lesions were associated with VUR is unknown because the observations were made before the introduction of radiocontrast cystography. Similar renal lesions in hypertensive children, some of whom were studied for VUR, were often, but not always, associated with VUR and urinary tract infection (UTI). For nearly two decades, these aglomerular lesions were referred to as segmental renal hypoplasia, which implied a localized failure of normal metanephric development. Finally, a series of patients whose kidneys had segmental renal lesions similar to Ask-Upmark kidneys and to segmental renal hypoplasia were observed in serial radiographic and pathologic studies; most of these patients had VUR as well as documented UTI [4]. Careful dissection in some of these kidneys revealed parenchymal lesions in various stages of development – acute inflammatory lesions only days old adjacent to completed aglomerular scars with no evidence of inflammation. It became quite evident that the aglomerular grooves or hypoplastic segments, described previously, were actually atrophic parenchymal scars resulting from localized pyelonephritis in previously normal renal tissue that had contained glomeruli and tubular structures. These lesions could now be referred to, more correctly, as *segmental renal atrophy* [11].

The proposed mechanism for pyelonephritis in humans has been that bacteria, multiplying rapidly in bladder urine, cross an incompetent ureterovesical junction as intravesical pressure increases during micturition. The inoculum reaches the renal pelvis and calyces, enters the papillary collecting tubules in one or more renal pyramids through the ducts of Bellini – intrarenal reflux (IRR) – and causes suppurative inflammation. The resulting injury may heal by scarring, and even a single scar may be associated with severe hyperten-

sion later in life. When scarring is more extensive and both kidneys are damaged, not only hypertension, but also chronic renal insufficiency or end-stage renal disease (ESRD) may develop. Although characteristic radiographic findings and histopathologic features of RN may be observed in kidneys never known to be infected or subjected to VUR, such cases have been considered unusual.

Once the relationship of renal injury to VUR was established, it was reasonable to think that eliminating VUR by surgery could prevent subsequent episodes of pyelonephritis and its clinical consequences. Clinical efforts over more than 30 years produced about 3,000 published reports on VUR and UTI [20]. Most so-called studies were focused on surgical techniques for restoring competence to the ureterovesical junction. When appropriate clinical trials were finally completed, just in the past decade, surgical correction was found to offer no advantage over conservative medical management in preventing renal scarring [13, 37]. Further understanding of the mechanisms whereby VUR injures the kidney acutely and initiates progressive injury without further infection, therefore, must come from future studies, not of the ureterovesical junction, but rather of the human kidney's responses to sterile injury as well as suppurative inflammation both before and after birth.

Incidence

The true incidence of RN is unknown. Perhaps the best evidence for RN being a distinct and, therefore, significant clinical problem is that it accounts for 15 – 25% of patients treated for ESRD in Europe and Australia/New Zealand [19]. There is no reason to think that the prevalence is less among patients with chronic renal insufficiency in North America, where RN has been shown to be a major cause of hypertension and ESRD in children and adolescents (Table 1).

Primary VUR includes only those patients in whom no other anatomic or functional abnormality can be identified and has been demonstrated in < 1% of humans with no prior history of UTI [2]. However, primary VUR will be found in 20 – 50% of children investigated following the first UTI (the highest incidence in the first year of life), 20% at 12 years of age, and only 5% in adults. A long-held notion has been that the incidence of VUR is higher when the voiding cystourethrogram (VCUG) is performed soon after an acute UTI, so the recommendation has been to wait for 4 to 6 weeks after the UTI to order the diagnostic study. Although no report has been made of the incidence of VUR between early and late studies within a single center, the incidence of VUR among children of various ages has not varied when studies at different centers were done either within the first week or more than 3 weeks following UTI [2]. There seems to be no merit in the practice of delaying a diagnostic VCUG once the urine has been rendered sterile, only to "minimize" the number of children with VUR. There may have been a time in the past when the diagnosis of VUR of any grade resulted in an attempt at surgical correction, but this is no longer the case. Today, children with UTI managed conservatively tend to get better clinical supervision, more education about the consequences of UTI and longer periods of follow-up when VUR is identified.

There is no gender difference in the incidence of primary VUR with UTI. The absolute number of girls with VUR is actually greater than the number of boys, but this is related more to the higher incidence of UTI in girls than boys after the first year of life. This

Table 1. Causes of ESRD in Pediatric Patients (Birth – 18 years old). UT Southwestern Medical Center at Dallas 1980 – 1989.

	n
Primary Uropathies	
Primary vesicoureteral reflux	19
Renal hypoplasia/dysplasia	14
Obstructive uropathy	14
Prune-belly syndrome	3
Neurogenic bladder	2
	52%
Glomerulopathies	
Focal segmental glomerulosclerosis	15
Rapidly progressive glomerulonephritis	3
Unclassified chronic glomerulonephritis	3
Membranoproliferative glomerulonephritis	3
Anaphylactoid purpura	2
Systemic lupus erythematosus	2
Hemolytic-uremic syndrome	2
Goodpasture syndrome	1
Congenital nephrotic syndrome	1
	32%
Miscellaneous	
Nephronophthisis	5
Autosomal recessive polycystic kidney disease	5
Neonatal cortical or medullary necrosis	3
Oligomeganephonia	1
Cystinosis	1
Hyperoxaluria	1
	16%
Total number of patients	100

incidence of VUR is similar among white, Hispanic and Asian children with UTI, but VUR is identified less often in black children. Moreover, RN is an unusual cause of hypertension or chronic renal insufficiency among black adolescents and young adults.

Primary VUR will be identified in 27 – 45% of asymptomatic siblings of children with VUR [36]. If one child in a family has renal scarring at the time primary VUR is found, the incidence of VUR in siblings may be even higher. As more genetic studies of families with VUR have been conducted, it would appear that primary VUR, with or without RN, does occur in multiple generations implying vertical transmission suggestive of a pattern of autosomal dominance with variable penetrance. A specific gene locus has not yet been identified. Scarred kidneys may also be associated with secondary VUR from anatomical obstruction as in posterior urethral valves, prune-belly syndrome, ureteropelvic

junction obstruction and urolithiasis, as well as from functional obstruction in a neurogenic bladder or with dysfunctional micturition – none of which are inherited problems.

One of the most common serious bacterial infection in infants and young children presenting with fever is UTI. Some general idea of the prevalence of RN in the general population can be learned from the frequency of a first UTI being, on average, 2.8% in children under five years of age. In the 1990 census there were 18,264,096 of these infants and young children in the United States. Therefore, approximately 511,394 children will have a first UTI by their fifth birthdays, and 30 – 50% or between 150,000 and 250,000 will, if examined, have VUR. The estimates of any degree of renal scarring from VUR and pyelonephritis – one simple scar, perhaps, or multiple scars involving one or both kidneys – have been reported between 12 – 50%, depending upon length of follow-up and methods used to assess renal scarring. The longer the follow-up and the more experienced the investigator, the more often renal scarring will be detected. Also, carefully performed intravenous pyelograms (IVP) and technetium-99m-dimercaptosuccinic acid (DMSA) renal scans found more scars than renal ultrasonography or poorly-done IVP. In a recent study of very young infants with acute pyelonephritis, for example, up to 40% of infants with VUR studied by DMSA scans six months after a UTI had some degree of renal scarring, but not all had VUR [24]. It will be important to follow these patients long-term to record the clinical significance of renal scars detected at this very young age.

If, for example, only 30% of infants and young children under 5 years of age with VUR and UTI develop renal scarring, there should be around 61,367 of them with RN. Assuming no renal scarring ever occurred after 5 years of age and no deaths among children and adolescents with renal scarring, approximately 368,204 people (3.3:1000) currently under 30 years of age in the United States alone should have RN. Only half of children recognized to have acute pyelonephritis, however, will have VUR demonstrated. One study found renal scarring following an episode of acute pyelonephritis in 37% of children without VUR [40]. Until recently, those children with UTI but without VUR have not been subjected routinely to follow-up renal imaging studies. Just how many of them will develop hypertension or renal insufficiency later in life is yet to be determined, but these patients will add to the overall incidence of RN in the general population.

More than half of children with a first UTI, with or without VUR, will experience another UTI within 6 months [31]. With each subsequent infection, the risk of renal injury is increased from 9% after the first UTI to 58% after the fourth [28]. A delay in effective therapy, which is not unusual in an infant or child whose complaints do not suggest UTI, can double the rate of scarring, and, therefore, increase the incidence of RN.

Despite opinions to the contrary, acute renal injury from pyelonephritis definitely causes scarring in children over 5 years of age – even in the absence of detectable VUR [10]. As children grow, VUR tends to resolve gradually in most infants and young children [20], while the incidence of UTI increases to 6 – 8% of school-age girls. Moreover, the rate of VUR resolution in these older children is slower. The consequences of secondary VUR, particularly in decompensated urinary bladders with recurrent UTI, as well as pyelonephritis complicating urolithiasis, only add to the total number of individuals suffering from RN. Perhaps the only reliable statement that could be made about RN to date is that its incidence has been underestimated – especially in the United States.

Etiology

RN has been attributed to pyelonephritis associated with VUR – more specifically IRR – in infants and young children (Figure 1). Few, if any, would argue that suppurative pyelonephritis can cause significant and permanent renal injury. The pathogenesis of renal scarring from VUR-associated pyelonephritis has been produced experimentally in animals either by injecting bacteria into the renal parenchyma or inoculating the bladder with fecal flora after VUR had been created. Shortly thereafter, one or more focal lesions of suppurative inflammation could be demonstrated in the renal parenchyma and, if effective antibiotic therapy was not provided within 5 days, renal scarring developed even though further bacterial growth was eradicated [38]. When treatment was delayed in children with UTI, the incidence of renal scarring was increased 4-fold over those treated promptly [49]. It seems that an inflammatory cascade is initiated by the bacteria within the renal parenchyma, much like that described for endotoxemia, which permits the inflammatory response to continue long after effective antibiotic therapy is introduced [39]. The evolution of the acute inflammatory lesions either to complete resolution or permanent scarring has been demonstrated by serial DMSA renal scintigraphy. Pyelonephritis caused by *P-fimbriated E. coli* seems related more frequently to renal scarring than some other common pathogens. The unique ability of this organism to attach itself to uroepithelium may allow it to cross the ureterovesical junction when VUR is not present and, perhaps, persist in the urinary tract longer than other bacteria.

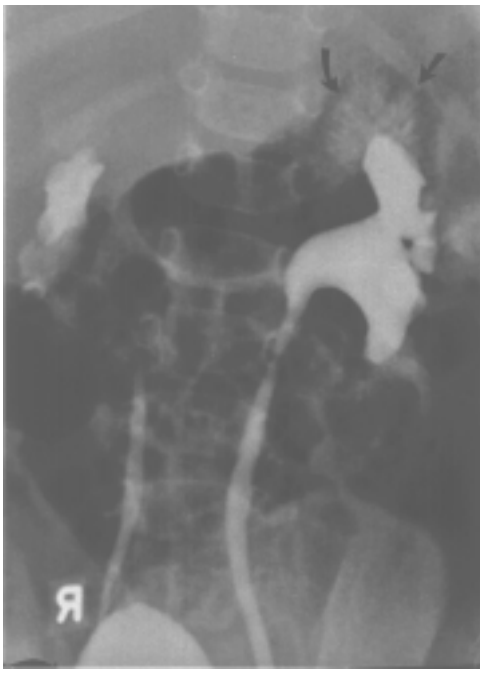

Figure 1. Intrarenal reflux (arrows) into the collecting ducts which extends into the outer cortex of the upper pole of a young girl's left kidney during voiding cystourethrography. There is no evidence of cortical thinning or scarring.

Whether sterile VUR can cause similar renal injury, however, is still actively debated. There is no doubt that typical atrophic renal scarring can be induced when sterile VUR is produced experimentally in animals, but the intravesical pressure required for scarring exceeds 60 cm water – higher than normal voiding pressures measured in children. Some will argue, therefore, that in the absence of bladder outlet obstruction or a decompensated, noncompliant bladder generating high intravesical pressures, renal injury is never associated with sterile VUR. The greatest argument favoring a role for sterile reflux, however, is the scarring associated with VUR in the fetal urinary tract where the urine is always sterile. The developing kidney of the fetus and young infant appears more easily damaged from VUR than does the kidney of an adult and probably older children as well. As more fetuses with dilated urinary tracts have been identified as having renal scarring associated

with VUR – not obstruction – at birth, it is hard to deny sterile VUR causes renal injury with scarring which is different from dysplasia. Segmental scars have been described in dysplastic kidneys subjected to primary VUR as well as obstructed urinary tracts [4]. When studied postnatally, a kidney with dysplasia will have the same ultrasonographic and, perhaps, DMSA scintigraphic appearance as the scarred kidney; however, an IVP will demonstrate segmental scars and calyceal deformities characteristic of RN even in abnormally small kidneys (Figure 2). Kidneys that are small from dysplasia alone will not excrete the radiographic contrast material, so the kidney will not be visualized by IVP. This limitation to more modern diagnostic imaging studies, now favored widely over IVP, is often overlooked as a means of establishing the diagnosis of RN in small kidneys.

Just what kind of intravesical pressure is "normal" for human infants and children? Before toilet training, intravesical pressures generated in normal bladders during micturition rarely exceed 35 cm water. On the other hand, during or after toilet training, when young children are rewarded for postponing micturition or, on their own, delay bladder emptying to continue playing or engage in other activities, intravesical pressures can easily exceed 35 cm water. Add to this any increase in intra-abdominal pressure that will increase intravesical pressure further, as would occur when the child jumps down steps, lands prone in a fall or coughs vigorously with a respiratory illness, and intravesical may exceed 100 cm water. Moreover, there is little dampening of pressure transmitted from the bladder to the renal pelvis across a refluxing ureterovesical junction. A distinct group of young children, for reasons yet unexplained, suffer from dysfunctional micturition, where there is poor coordination of sphincter relaxation during bladder contraction. Higher than normal intravesical pressures may reach 200 cm water in some children both during and between attempts at micturition. Recurrent UTI, which is typical in children with dysfunctional micturition, adds to the incidence and severity of renal injury. Other symptoms of dysfunctional micturition include infrequent micturition, dysuria in the absence of UTI, diurnal incontinence, nocturnal enuresis and constipation. This condition is complicated by VUR, but when unrecognized and inadequately treated,

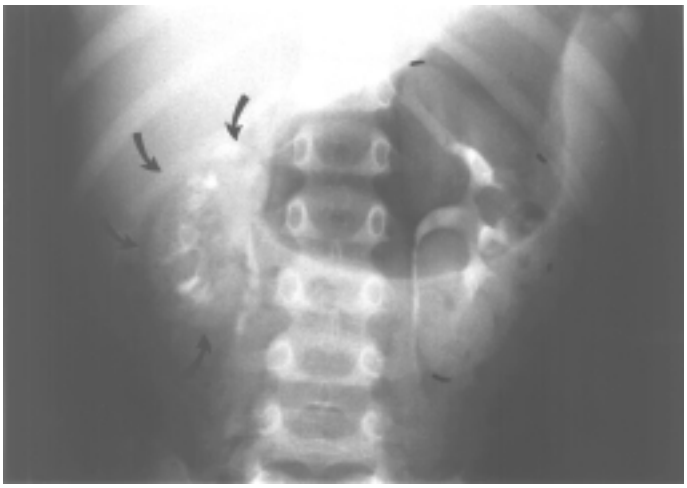

Figure 2. Intravenous pyelogram in 3 yo male discovered to have right Grade II vesicoureteral reflux following a first recognized urinary tract infection. There is generalized cortical atrophy (arrows) in the abnormally small right kidney with deformed calyces. Note how well the small kidney excreted the contrast agent that is typical of chronic atrophic pyelonephritis or reflux nephropathy. The left kidney is unusually large because of compensatory hypertrophy, but is otherwise normal.

VUR fails to resolve spontaneously as it does in other children, and anti-reflux surgery often fails.

Statements have been made that only IRR can cause renal injury. When the renal pelvis of either the human or animal kidney was filled with contrast material under pressure, the contrast solution was found not only to enter the papillary collecting ducts but also to traverse the length of the entire nephron reaching Bowman's space. Because IRR is rarely identified or, perhaps, recognized when a voiding study is done, the conclusion stated in many references is that the actual incidence of IRR is low. Again, this problem is relative only to the detection of IRR which, when seen, is a transient phenomenon at peak voiding pressure (Figure 1). The frequency of IRR being identified is directly related to the interest and skill of the observer performing the VCUG. If renal scarring were possible only with IRR, but IRR is never identified – even in repeated studies – then an entirely new, alternate mechanism for the development of segmental renal lesions must be tendered.

Renal scarring is most evident on diagnostic imaging studies in either upper or lower poles. The porcine model of the refluxing kidney was favored by some investigators because, like the human kidney, the pig kidney has compound papillae draining polar pyramids. The assumption was that IRR occurred more easily in these compound papillae; however, scarring occurs frequently in association with simple papillae as well and in the mid-region of kidneys where small scars seem more difficult to detect by IVP or ultrasonography. Another popular hypothesis advanced 20 years ago was the *"Big-Bang theory"* which meant that the kidney was scarred, sometimes irreversibly, after a single episode of infected IRR. For example, one month following a first UTI, the right kidney of a 3-year-old child with mild (Grade I) VUR was normal (Figure

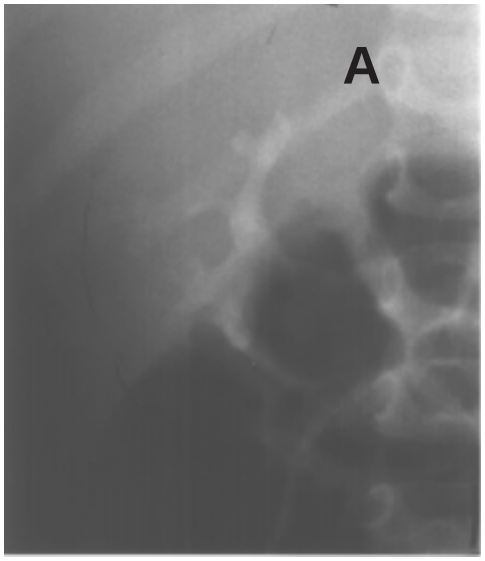

Figure 3a.

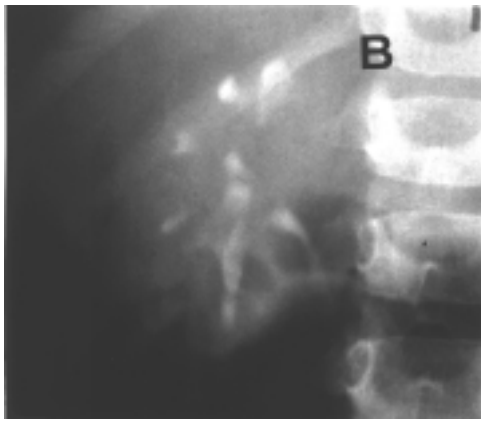

Figure 3b.

Figure 3. The appearance of the right kidney (A) was normal following the first urinary tract infection in a 3 yo female who had right Grade I vesicoureteral reflux. One year later, during which the urine was documented to have remained sterile and the reflux had not worsened, the same kidney (B) is reduced in overall size from 4.5 to 3.0 vertebral bodies due to cortical atrophy. The calyces in all regions exhibit the swallowtail deformity of chronic atrophic pyelonephritis or reflux nephropathy.

3a). One year later, VUR remained mild, compliance with conservative management including antibiotic prophylaxis was good and the urine had been confirmed sterile by culture at regular intervals. The kidney, however, was reduced to approximately half its previous size and exhibited generalized renal scarring with calyceal abnormalities (Figure 3b). On the other hand, new and progressive scarring over several or many years have been reported often in patients subjected to serial IVP during follow-up for VUR [37]. The histopathologic identification of lesions in various stages of development supports the idea that multiple scars may result as well from a *"series of little bangs"* [12]. This latter hypothesis appears to have support from the increase in the incidence of renal scarring with recurrent pyelonephritis [28].

It is widely accepted that the prevalence of renal scarring among all patients with VUR is related directly to the grade of VUR observed during voiding cystourethrography. When VUR is associated with a dilated collecting system (International Grades III – V), renal scarring will be noted in 28 – 50% of kidneys. The number of scarred kidneys associated only with non-dilating VUR (Grades I – II) is usually overlooked because the incidence of scarring is only about 10%. Many seem willing to attribute the renal injury in children with lesser grades of VUR to an earlier time when "VUR must have been more severe" because VUR tends to resolve in most, if not all children, with time and continued growth. When infants and young children with radiographically normal kidneys were followed in serial studies for 5 years after their first recognized UTI, 28% of kidneys subjected to grade III VUR were scarred while only 10% of kidneys with grades 0, I and II VUR had scars [3]. The importance of these observations is not that the incidence of renal scarring was less with mild and moderate VUR, but rather that the total number of scarred kidneys is greater because more patients have mild and moderate VUR than severe VUR. The consequences of renal scarring from any grade of VUR should not be ignored.

Case Presentation

Following her first recognized UTI, a 3-year-old white female was found to have Grade I VUR on the right. Both kidneys were normal by renal ultrasonography. There was no additional UTI, but 5 years later, the patient presented to an emergency department with heart failure. Her blood pressure was 210/160 mm Hg. Once her hypertension was controlled, the heart failure abated. Evaluation revealed Grade I VUR still on the right – no change in 5 years. However, the IVP revealed a single scar in the upper pole of the right kidney.

There has been a long running debate over whether renal scarring from UTI and VUR ever occurs after 5 years of age. In fact, some would argue that all renal injury is initiated by VUR *in utero* and detected only when diagnostic imaging is performed postnatally following the first UTI. Others have claimed that renal scarring never results from VUR and UTI and that so-called scars are actually areas of renal dysplasia. Certainly, most patients with recognized RN have a history of UTI in early childhood. A recent retrospective study could identify few scars by DMSA scintigraphy to develop in children with VUR after 4 years of age [48]. One prospective study in children of all ages found no renal scar to develop beyond 2 years after the last episode of pyelonephritis [13]. On the other hand, 2 other prospective studies noted new scars not only later than 2 years from the last febrile UTI but also to occur in subjects older than 5

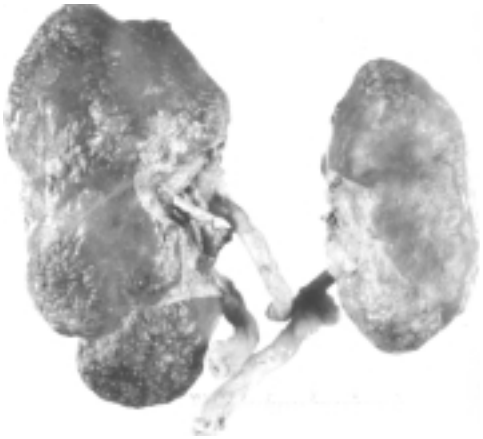

Figure 4. Both kidneys were removed from this 14 yo female before transplantation. Grade III vesicoureteral reflux was demonstrated into both ureters of the duplicated but unobstructed right collecting system as well as the single left ureter. This girl presented at the age of 9 years with hypertensive encephalopathy and had only one recognized prior urinary tract infection. In spite of satisfactory control of her hypertension without ACE inhibition, surgical repair of her reflux, and sterile urine, progressive deterioration in renal function was observed over the next 5 years (see Figure 11, upper panel, square symbols labeled SR).

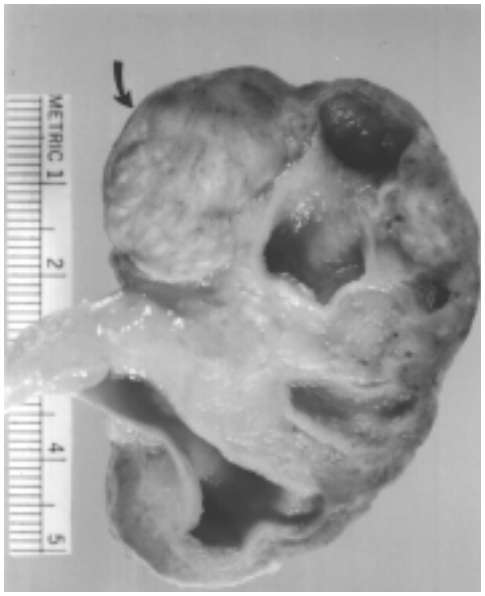

Figure 5. The left kidney from a 13 yo female who presented with ESRD and no evidence of prior hypertension or urinary tract infection. A thin rim of aglomerular parenchyma was present over each calyx. In the upper pole an unscarred pyramid (arrow) had evidence for compensatory hypertrophy and what was responsible for most of her residual renal function. There was no histopathologic evidence of renal dysplasia.

years of age [3, 37]. Recently, adolescent patients with febrile UTI – a group rarely subjected to diagnostic imaging – were studied by DMSA scintigraphy. The rate of renal scarring was compared in infants (43%) and found actually to be higher in young children (84%) and adolescents (80%) [10].

Pathology

The gross morphologic appearance of kidneys scarred by pyelonephritis associated with VUR is illustrated in Figure 4. The kidney is usually reduced in weight as well as overall dimension if scarring is extensive. When there is only one or, perhaps, 2 segmental scars, however, the kidney may otherwise appear normal. Any irregular contour of the uncut kidney's surface is due to areas of segmental atrophy separated by unscarred parenchyma that has undergone compensatory hypertrophy. When the scarring is mainly in polar regions, the mid-portion of the kidney may have a nearly round appearance because of the compensatory growth in unscarred pyramids. When the kidney is bisected longitudinally through the pelvocalyceal system (Figure 5), scarred areas can be seen to overlie a dilated or deformed calyx. Pelvocalyceal dilatation is not a constant finding in RN. The histopathologic features of RN will be missed if the pathologist, hoping to find renal tissue

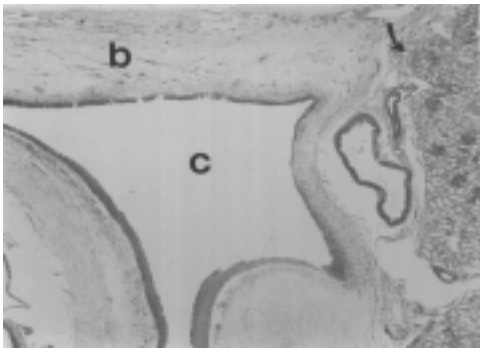

Figure 6. Microscopic examination of the aglomerular fibrous band of tissue (b) overlying a calyx (c). The segment is well demarcated from the normal renal cortex with glomeruli and tubular structures to the right of the calyx (arrow). (PAS stain; 18x magnification).

not yet completely destroyed, examines only sections from the most normal looking areas. To make the diagnosis of RN, a section for microscopic examination should be taken across a scar to include both the adjacent, more normal appearing parenchyma, as well as the underlying calyx.

Microscopically, a completely atrophic scar will be seen as an aglomerular band of tissue overlying a calyx (Figure 6). This band represents once normal renal cortex and medulla injured when IRR, with or without infection, disrupted the collecting duct epithelium and caused local inflammation. The inflammatory response irreversibly damaged either the medullary or papillary collecting ducts associated with those nephrons, the post-glomerular medullary vessels, or both. In time, the segmental injury causes loss of normal histology with the lesions variably containing atrophic tubules, tubular microcysts, sclerotic glomeruli and arcuate vessels separating the atrophic cortex from the atrophic medulla [4, 11]. Depending on the timing of the histologic examination after the injury was initiated, the various phases of acute tubular disruption with mild to marked inflammation – even pus – may be found in proximity to a much older, completely atrophic lesion, especially in a kidney which has been or continues to be injured repeatedly over a period of years. The lesions of RN have been identified even in patients whose VUR was surgically corrected years before the kidney was removed [12]. Other histopathologic features of RN may include renal dysplasia in kidneys subjected to intrauterine VUR or obstruction during metanephric development, but kidneys injured only after birth should not contain dysplasia [4]. When one kidney is scarred in RN, the contralateral kidney, if never subjected to VUR or infection, may exhibit focal glomerulosclerosis [29]. This finding suggests a humoral mechanism by which injury to one kidney can cause changes in the opposite kidney. Based on studies of remnant kidneys focal glomerulosclerosis in RN may be explained better as evidence of glomerular hyperfiltration. A very good candidate for the circulating factor may be angiotensin II (Ang II) produced either after renin is released in increased amounts from the scarred kidney or to increased efferent arteriolar resistance and glomerular filtration by the normal kidney.

Diagnosis

Confirming the clinical diagnosis of RN in any given patient requires a high index of suspicion. Firstly, one must believe that the renal lesions associated with VUR represent a distinct pathologic entity. Distinguishing the problem from other clinical entities, in which a kidney may also be small, requires a certain familiarity with the specific features of RN. A

history of UTI or VUR in a sibling should alert the clinician to the possibility of RN. The medical history of a patient with RN is important, but the physical examination is usually unhelpful unless the patient already has developed complications of renal scarring, particularly hypertension and its clinical consequences. Not all patients presenting with RN will have had a UTI recognized in the past and, if so, will not have had radiographic investigation to document the presence of VUR. This was the case of the 13-year-old white female who presented with ESRD and normal blood pressure; one of her kidneys is pictured in Figure 5. The absence of VUR, particularly in older children with UTI and renal scarring, does not guarantee that VUR was never present because the natural tendency is for VUR to resolve with age [3, 20].

One or more febrile UTIs in infants and young children, with or without VUR, place them at risk of renal injury with subsequent parenchymal scarring. A longer interval between the clinical onset of pyelonephritis to the first dose of an effective antibiotic will increase the chance for renal scarring [49]. With recurrent UTI, the incidence of renal scarring increases from 9% after the first UTI to 58% after the fourth [28]. When VUR is detected, renal scarring can be expected to be present or develop in 50% of children with severe VUR (Grades IV and V), 28% with moderate VUR (Grade III) and in 10% of mild VUR (Grades I and II) [3, 44]. Symptoms of dysfunctional micturition such as diurnal incontinence, infrequent and incomplete micturition and constipation, mostly in females, imply higher intravesical pressures, persistent dilating VUR, recurrent UTI and a greater likelihood of renal scarring.

Voiding Cystourethrography (VCUG)

Clinical recommendations have been made consistently in general pediatrics, pediatric nephrology and urology literature for more than 50 years that each infant or child with a first febrile UTI undergo radiologic investigation to detect an anatomic or functional abnormality which may cause further damage to the urinary tract [34]. In addition, boys at any age and girls under 3 years of age should be studied following the first UTIs whether it is symptomatic or not. More recently, the recommendation has been made to investigate asymptomatic siblings of children with VUR – at least those < 5 years of age – in the hope of detecting VUR before the first UTI can occur [36]. These directions have been followed reluctantly by some and inconsistently by others. The principles of treating cystitis in sexually active women often prevail in managing UTI in children, particularly when the physician is not a pediatrician. There seems to be an aversion by many parents to subject their child to the perceived emotional and physical trauma of bladder catheterization. Substituting renal ultrasonography for the cystogram may identify an upper tract abnormality, like a dilated calyx or advanced cortical atrophy, but will not eliminate the possibility of VUR [14]. When the child's physician is not convinced of its value, the workup is often not pursued.

Until recently, contrast VCUGs were done initially and as frequently as every 6 months during follow-up of a patient with VUR. In the past, when VUR worsened or a renal scar was noted, surgical correction of the VUR was recommended. Upon learning from prospective clinical trials that all grades of VUR either resolved spontaneously or the renal outcome could not be altered appreciably by surgical intervention, whether or not the kidney was

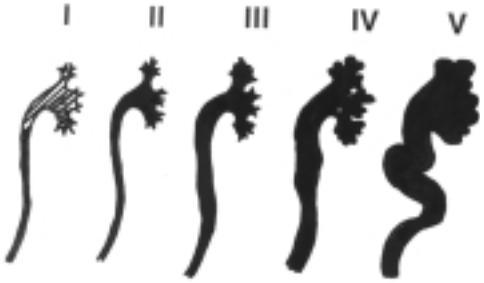

Figure 7. Grading of vesicoureteral reflux according to the classification of the International Reflux Study in Children. The black areas of the collecting system represents contrast material from the bladder, which flows retrograde across the ureterovesical junction during micturition. If the contrast material enters the ureter but does not reach the renal pelvis, Grade I is assigned. When the contrast material fills but does not distend either the ureter, pelvis or calyces, Grade II is assigned. If either the pelvocalyceal system or ureter is distended, reflux is considered Grade III. In Grades IV and V, the ureter becomes progressively more tortuous, the pelvis is more dilated and the calyces are more blunted, losing their papillary impressions.

already scarred, follow-up radiographic studies were ordered less often. A more sensitive test to detect VUR is the radionuclide cystogram, which is recommended for all females, for sibling screening and for follow-up studies. Grading VUR as being more than dilating or non-dilating is not possible with radionuclide cystography, but this does not diminish its clinical value. The contrast VCUG is still recommended for the first study of the male bladder to detect posterior urethral valves. Either type of cystographic study should include observations after the catheter is removed and during micturition when intravesical pressure is highest and the possibility for VUR being detected and graded in a standardized fashion is more likely.

Through the years, there have been 3 or more different grading classifications of VUR. The classification used by the International Reflux Study in Children has now replaced all others and facilitates comparison of data from one study to another (Figure 7). The grading of VUR should be done under standardized conditions. The bladder is gradually filled, but not overdistended, at 70 cm water pressure. If VUR is observed before the bladder is filled with radiocontrast or radionuclide material, the reflux is said to occur when intravesical pressure is low. When VUR is noted only during micturition, the reflux is considered to occur at high intravesical pressure only. The grading of VUR depends on whether the contrast or radionuclide reaches the renal pelvis; if it does not, the VUR is grade I. If the reflux fills but does not distend the ureter or renal pelvis, it is grade II. Grades III, IV and V depend on the extent to which the collecting system is distended by VUR and how tortuous the ureter has become – an effect of dilating VUR and time. An acute distention of the collecting system by an overly aggressive filling of the bladder can cause mild VUR to be assigned a higher grade. A renal ultrasound examination or IVP done before or sometime after the VCUG will, in this case, not show the collecting system to be dilated. When studied subsequently, the VUR may have "improved" or even have resolved if the intravesical pressure remains normal during the procedure. Patients whose collecting systems by IVP or renal ultrasonography are dilated and who exhibit grades III, IV or V VUR usually have long-standing reflux that may have been originally under high pressure. Once the collecting system is damaged, however, the benefit of elastic fibers and smooth muscle layers do not permit its return to its former caliber, and VUR will occur even at low intravesical pressure. The grade of VUR in these ureters is much less likely to improve even after many years of observation.

While great importance has been paid and much time spent on the grading of VUR, it is probably enough to know whether the VUR

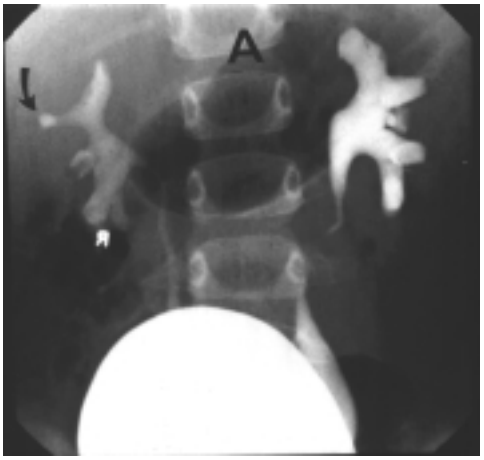

Figure 8a.

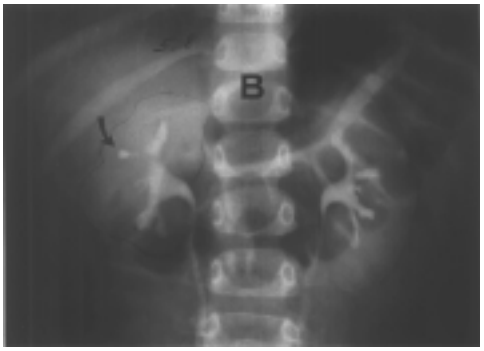

Figure 8b.

Figure 8. Bilateral vesicoureteral reflux, Grade III on the right and Grade IV on the left, noted during a VCUG (A) in a 2 yo female following her second recognized urinary tract infection. The renal ultrasound examination was reported as normal. Because the calyces were deformed on the voiding study, an IVP (B) was performed and revealed cortical atrophy on the right with the very same calyceal deformity (arrows).

caused dilatation of the collecting system or not – a reflection of the intravesical pressure and, perhaps, the pressure exerted at the ducts of Bellini to cause IRR. When VUR causes the entire collecting system to be filled completely (Grade II or higher), the calyceal abnormality associated with scarring is often identified and, if the renal outline is seen well, parenchymal thickness over the calyx can be assessed. These findings, when present, are important and should never be overlooked – the VCUG is not just a VUR detecting study. In Figure 8, the same calyceal deformities and parenchymal thickness over the calyx can be appreciated on both the VCUG (Figure 8a) as well as the IVP (Figure 8b).

Intravenous Pyelography (IVP)

The standard IVP was the diagnostic study done most often in the initial, and usually annual, evaluation of patients with VUR to detect scarring. While imaging studies introduced more recently may be more convenient, as with renal ultrasonography, or more sensitive in detecting renal injury earlier, as claimed for DMSA scintigraphy, IVP remains the best and, sometimes, only test available which depicts the anatomy of the calyces, renal pelvis and ureters. The history of allergic reactions to the contrast material used before the availability in most centers of non-ionic preparations, now used in most centers, has been another excuse used to forego the IVP. The sensitivity of identifying significant renal injury among the various studies depends more on the experience of the technician/observer than on the inherent superiority of the study itself [45]. Although many radiologists have abandoned the practice of bowel preparation before an IVP is done, it is still essential to empty the colon of feces to assure good visualization, especially of the renal parenchyma, but also to see the collecting systems well. Feces in either flexure of the colon may obscure a renal cortical defect or abnormal calyx. To further improve the quality of the imaging, the patient should be hydropenic

(thirsted until the urine specific gravity is > 1.025, or 8 – 12 hours, except in infants), and the volume of contrast material should be injected in age-related doses to get a good nephrogram on a film at 1 – 3 minutes after injection. Subsequent films should be obtained to visualize the contrast-filled pelvocalyceal systems and ureters. The characteristic renal lesion of RN will be thinning of the renal cortex overlying a calyx that may or may not be abnormal. As originally described, the calyx associated with the scar was referred to as a swallowtail deformity [25] (Figure 8). Basically, this calyx has no papillary impression and, when filled by the excreted radiographic contrast material, no longer has its normal appearance, which resembles a white china teacup.

The radiologic diagnosis of a renal scar should be suspected when a calyx is clearly abnormal or deformed either on IVP or VCUG (if VUR is present), when the renal length or parenchymal surface area is > 2 standard deviations (SD) below the recognized mean size for age or height, or when there is a discrepancy between the lengths of the right and left kidneys of > 0.5 cm. A scar may be present when the renal cortex is thin in one area (> 2SD below the mean normal value), usually overlying a calyx which may or may not be deformed [37]. The two-dimensional measurement or planimetric surface area (PSA) of the kidney will give important information for determining whether there has been any reduction of functioning renal parenchyma compared to normal, especially when renal injury has resulted more in poor renal growth rather than discrete segmental scarring [16]. Changes in the combined PSA of both kidneys have been correlated well to changes in glomerular filtration rate (GFR) [1]. There may be little difference between the apparent thickness of the scarred segment and the adjacent normal renal tissue especially in infants whose cortical height may be ≤ 10 mm. When the normal renal parenchyma on either side of the scar grows or undergoes compensatory hypertrophy, the scarred segment – which does not grow – may be noted on the next IVP [42]. Even when done carefully and interpreted by an experienced observer, the IVP may not show convincing evidence of renal scarring for 6 months to 6 years after the diagnosis of VUR was made, especially in infants and young children [4]. Suggestive evidence of renal scarring, which may precede the detection of a definite renal scar, is a discrepancy in size between kidneys. The kidney with scarring may be smaller than normal, while the contralateral kidney, if truly unaffected, will be larger than normal because of compensatory hypertrophy (Figure 2). If the PSA of the two kidneys were combined, the total PSA (scarred + normal large kidneys) may actually be normal, as will overall renal function.

Renal Ultrasonography

The factors of convenience and safety provide the basis for recommending that renal ultrasonography is preferable for diagnostic screening of at least the kidney and upper urinary tract of children with UTI. In fact, the suggestion that the ultrasound exam be the only diagnostic study for a child with febrile UTI has been made, but is not yet widely accepted. The basis for this recommendation has been that when kidneys appear normal following a UTI and the collecting systems are not dilated, then it matters little whether the patient has VUR because management will be directed at preventing further UTI, rather than deciding for or against surgical repair of VUR. There is some merit to this proposal. However, ultrasonography is rela-

tive insensitive at detecting all but severe renal scarring and does not identify VUR unless the collecting system is dilated – even then one study reported the sensitivity to be no more than 25% [14]. Dilated calyces are often mistaken for simple renal cysts (Figure 10a). For those who have relied on knowing whether VUR is present, not knowing about the status of the VUR presents a clinical dilemma.

Case Presentation

A white female had 2 recognized UTIs with fever and several other episodes of unexplained fever treated with antibiotics before her first radiologic investigation at 4 years of age. The renal ultrasound was reported to be normal, and no VUR was detected on a radionuclide VCUG. The patient was treated with antibiotic prophylaxis for one year without breakthrough UTI. Once the treatment was discontinued – the patient had no VUR and the ultrasound was normal – a febrile UTI occurred within 2 months. After appropriate antibiotic treatment for the acute pyelonephritis, prophylaxis was prescribed again for 6 months, and the patient remained free of UTI. After stopping daily antibiotic therapy, the patient had another febrile UTI one month later. Re-evaluation of the patient at 6 years of age revealed both kidneys to be "normal" by ultrasound (Figure 9a) except that the length of the left kidney (6.4 cm), which at 4 years of age had been at the lower limit of normal, had not changed during the 2 years between the studies and was 6.6 cm (> 2SD below the mean normal value for age). The right kidney measured 8.1 cm and had grown normally. A DMSA renal scan was performed to investigate the small left kidney (Figure 9b). Extensive parenchymal scarring of the upper and lower poles of the left kidney was identified. Careful re-evaluation of both renal ultrasound studies revealed no evidence of renal scarring other than the small size of left kidney. Had the variable of renal size been overlooked, which is all too often the case, this patient would have been considered normal and appropriate follow-up for a child with a scarred kidney would not have been planned.

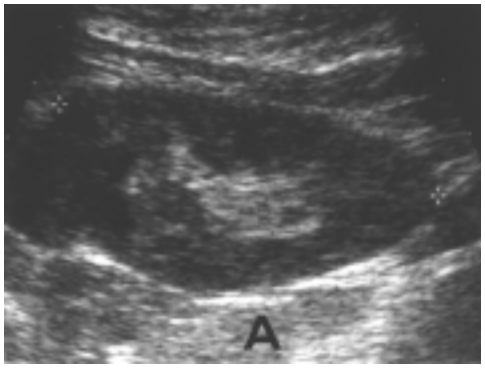

Figure 9a.

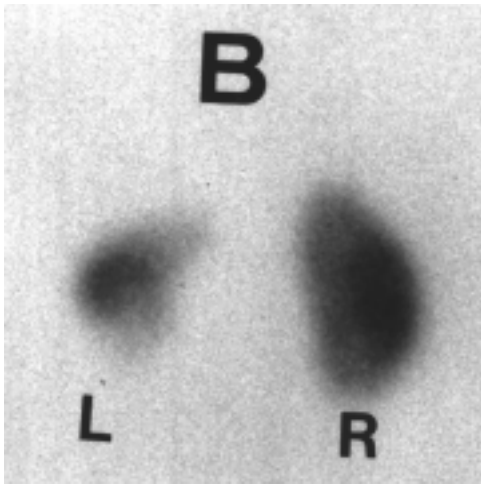

Figure 9b.

Figure 9. Renal ultrasound examination of the left kidney in a 6 yo female with a history of recurrent urinary tract infection. The overall appearance of the image (A) is normal but the length (+) was 6.4 cm (> 2 SD below normal mean length for age). A DMSA renal scan (B) revealed extensive scarring of both upper and lower poles of the left kidney.

Technetium-99m-Dimercaptosuccinic Acid (DMSA) Scintigraphy

The DMSA scan offers less radiation than conventional urography, is much more convenient for the patient, requires no bowel preparation or fluid restriction and has little or no risk of an allergic reaction. The shortcomings of the DMSA renal scan include an inability to estimate renal size or function or to assess calyceal morphology. Moreover, the DMSA scan takes a minimum of 3 hours, is expensive – about twice that of the IVP or renal ultrasound examination – and has what is probably too much interobserver variability. Individual observers may be consistent with their interpretations of DMSA renal scans only about 85% of the time, but the interobserver variability may be even greater. Some clinicians have recommended a DMSA renal scan be performed during an acute episode of UTI to confirm the diagnosis of pyelonephritis. Then, a follow-up DMSA scan at least 3 months later, after acute inflammatory changes have resolved, will confirm the presence of any renal scarring in the areas of inflammation noted on the original study. Managing the costs of such recommendations may prove problematic in the future. Moreover, knowing renal parenchymal inflammation is present in a febrile child with significant bacteriuria will have no impact on clinical decision for treatment. Recently, 40% of infants [24] and 80% of children and adolescents [10] with febrile UTI were found to have renal scarring by DMSA studies done 2 – 6 months later. There are no long-term data on the outcome of scarred kidneys identified so soon after acute injury.

There are now just about as many opinions for how UTI in children should be evaluated as there are physicians treating them. While clinicians more experienced with the management of UTI and VUR in children may have held on for too long to outdated ideas, inexperienced observers – especially non-clinicians who perform meta-analyses on other people's incomplete data – are recommending radical departures from conventional approaches. One such meta-analysis [17] concluded that there was no correlation between diagnostic imaging and clinical outcome in patients with UTI – an obvious notion, just as there would be no expected relationship between bone marrow aspiration and the outcome of patients with leukemia. Because there has been little progress to date in preventing renal scarring associated with UTI and VUR, several reports have recommended little or no investigation be done to detect VUR or renal scarring – just treat the UTI when it occurs. After a careful and extensive review of the medical literature for the past 30 years, the American Urological Association published a report to give clinical guidelines, especially for urologists but for other physicians as well, to standardize the diagnostic approach and clinical management of children found to have VUR following a first UTI [20].

Clinical Outcome

The natural history of acute pyelonephritis can be characterized from clinical descriptions in the pre-antibiotic era as fever and flank pain lasting 4 – 7 days. Subsequently, the patient either died from urosepsis or became entirely asymptomatic. Many of those who apparently recovered from acute pyelonephritis exhibited recurrent bouts of "suppurative nephritis" and died years later, sometimes of heart failure or stroke. When

indirect measurements of arterial blood pressure came to be measured more routinely about 60 years ago, there was a clinical debate over what the upper limits of normal systolic blood pressure should be – 120 or 140 mmHg. The higher limit was accepted. Nevertheless, it became possible in autopsy series to correlate antemortem hypertension with its cardiorenal complications. A direct relationship between pyelonephritis and hypertension was established more clearly when nephrectomy in unilateral renal scarring was followed by an abrupt return of the blood pressure to normal. Of particular interest was the frequent finding of pyelonephritis in patients who had succumbed to cardiovascular disease that likely was secondary to unrecognized or untreated hypertension. Effective pharmacologic control of hypertension and, therefore, prevention of its cardiorenal consequences became possible only in the past 30 years. Recently, the upper limit of normal blood pressure which appears to afford some cardiorenal advantage – 125 mmHg – seems to be closer to the recommendation of the losers in the original debate.

Hypertension

The cause of sustained hypertension in 26% of adolescents at one U.S. center [5] and in 35% of children referred to a single center in the U.K. [18] was renal scarring or RN. Hypertension has been detected in up to 50% of adults with RN [30], depending, again, on how long patients with renal scarring were seen for follow-up evaluations. In one series, hypertension was detected, on average, 8 years after the diagnosis of VUR was made and 2 years after the first renal scar was detected on serial IVP [42]. Another study found hypertension 27 years after the diagnosis of VUR was made [26]. The most common presentation of RN-associated hypertension in women is encephalopathy or heart failure which usually occurs around puberty, when taking birth control pills or during pregnancy: all periods associated with increased estrogen. Estrogen is thought to increase the production of angiotensinogen, at least during pregnancy. Many women are unaware of their RN before their hypertension is identified. For reasons yet unexplained, hypertension from RN is less common in adolescent males. The mechanism for hypertension in older adults with renal scarring, mainly from pyelonephritis associated with urinary tract obstruction or urolithiasis, may be multifactorial and requires a slightly different kind of clinical evaluation and management.

Hypertension in RN is angiotensin mediated and easily controlled in most cases with an ACE inhibitor or AT_1 receptor blocker given once daily. Plasma renin activity (PRA) in the segmental venous drainage of a renal scar has been demonstrated, whereas the PRA from blood sampled only from the main renal vein may be normal, owing to its dilution with blood draining normal areas of the kidney [27]. The resulting increase in angiotensin production raises vascular resistance and pressure in both the systemic and renal circulations. The hypertension may not produce recognizable symptoms often until there is headache, a disturbance in visual acuity, seizure activity, heart failure, or stroke. Retinopathy consisting of arteriolar changes, hemorrhages, cotton wool spots and papilledema will be noted on physical examination in many patients. Moreover, concentric hypertrophy of the left ventricle will be detected by echocardiography. The duration of sustained hypertension required to produce these changes before severe symptoms necessitate a precipitous evaluation is not known, but it is thought to be at least 2 months and

maybe longer. Before the availability of reliable treatment, not every case of severe hypertension in adults was associated with retinopathy for as long as 2 years of more. Unsuspected and uncontrolled hypertension may itself damage the scarred kidney further and accelerate deterioration of renal function as recognized for many years in patients with malignant nephrosclerosis.

Case Presentation

A typical presentation in which the diagnosis of RN was missed initially is illustrated by the following case. A 15-year-old white female was treated by a gynecologist for severe menorrhagia and anemia with blood transfusion and an oral contraceptive agent. The patient's blood pressure was 100/68 mmHg at the outset of treatment. Within a month, the patient began to complain of blurred vision that worsened over several months before she presented to the emergency department with encephalopathy, retinopathy including papilledema and a blood pressure of 260/140 mmHg. A CT scan of the head was reported to be normal. The only biochemical abnormality detected was a serum creatinine concentration of 2.0 mg/dL, which represented an estimated reduction in overall kidney function to < 50% of normal. In an adult critical care setting, the patient's blood pressure was lowered, but not well controlled, first by nitroprusside then by nitroglycerin with the addition of labetalol and clonidine. Nevertheless, the encephalopathy improved. Further evaluation included renal ultrasonography which was interpreted as normal except for a small "cyst" in the outer renal cortex (Figure 10a) No observer appreciated that the length of each kidney (8.3 cm and 8.8 cm) was > 2 SD below the normal mean length for age [22]. Selective renal arteriography revealed no vascular abnormality and was considered normal, except for what appeared to be fetal lobulations bilaterally, (Figure 10b). Because no renal arterial lesion was identified, delayed films were omitted, so the pelvocalyceal systems were never visualized.

Upon discharge from the hospital, the parents consulted yet another physician because the blood pressure was poorly controlled on increasing doses of clonidine and labetalol. The patient's school performance had deteriorated, and she was sleepy during the day despite adequate sleep at night. After reviewing the patient's prior records, the physician noted the small size of both kidneys and ordered an IVP to "complete" the angiographic study and demonstrated conclusively that the "fetal lobulations", which do not have such an exaggerated appearance in the mature kidney, really represented bilateral renal scarring. The segmentations in the renal cortex of both kidneys were immediately above abnormal calyces and the "cyst" noted on the ultrasound examination was, in fact, a dilated calyx (Figure 10c).

The estrogen-containing oral contraceptive agent was discontinued, and an ACE inhibitor was prescribed as monotherapy for severe hypertension. The patient's blood pressure has remained at 110/65 mmHg with enalapril 10 mg daily as the only medication. Within a month, the patient's school performance had returned to its previous superior level. Six months later, the concentric left ventricular hypertrophy had resolved. However, the serum creatinine concentration remained elevated at 1.6 mg/dL, meaning the patient is at high risk to experience further deterioration of renal function.

While all 3 studies either suggested or confirmed the correct diagnosis of RN, neither the internist who admitted the patient for hypertensive encephalopathy nor the various radi-

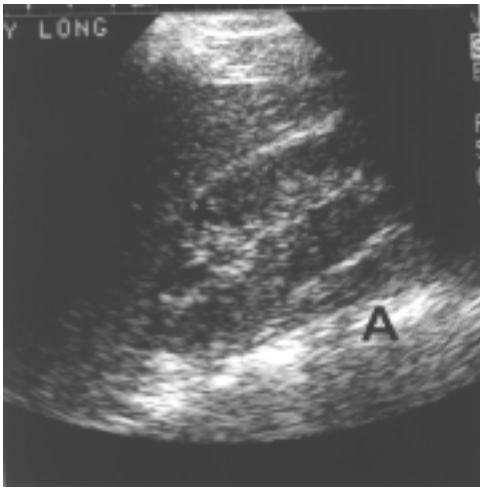

Figure 10a.

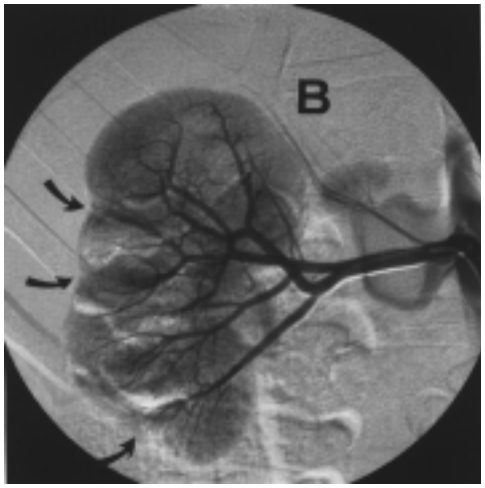

Figure 10b.

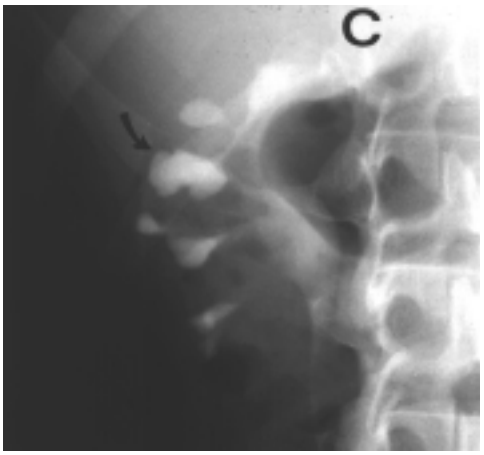

Figure 10c.

Figure 10. A 15 yo female presented with hypertensive encephalopathy. The renal ultrasound examination (A) was read as normal except for a "small cyst" (limits demarcated) in the upper pole of the right kidney. Selective renal angiography (B) was interpreted as normal with bilateral "fetal lobulations" (arrows; right kidney), but the study is characteristic of angiographic findings in reflux nephropathy. An IVP (C) demonstrated segmental cortical atrophy with deformed calyces – reflux nephropathy. The "cyst" noted on the sonogram (arrow) is actually a dilated calyx.

ologists performing the imaging studies appeared to be familiar with the typical presentation and diagnostic features of RN. Unfortunately, this clinical scenario is not uncommon. The absence of a prior history of UTI or recurrent febrile illnesses in the first years of life is not so unusual in patients with RN. Acute UTI at this age is not recalled by the patient and the parents may not recall the past medical history of the child or may not be available to provide such a history in adult patients. However, there is almost no other cause of hypertension with such a dramatic onset of symptoms in adolescent females soon after puberty, after estrogen-containing oral contraceptive agent is prescribed or with pregnancy.

Chronic Renal Insufficiency

Chronic renal insufficiency develops only in patients with RN who have bilateral, severe

renal scarring and may be recognized only when patients are examined for other problems, such as hypertension. The approximately 1% of patients born with a single kidney and those who lose a kidney after birth are at risk of a reduction in GFR with only unilateral renal injury from VUR or UTI. Undetected hypertension may, in fact, cause further injury to a scarred kidney and, itself, account for the development of chronic renal insufficiency – even ESRD. This deterioration in renal function might have been prevented had the hypertension been detected soon after its onset and treated appropriately. It is not unusual for scarred kidneys to exhibit deterioration of overall renal function > 20 years after the last episode of pyelonephritis [26] and after VUR has resolved or corrected surgically. Therefore, RN may be the cause of the large number of adult patients with small kidneys presenting with ESRD without a clinical diagnosis.

The overall prevalence of chronic renal insufficiency in RN is difficult even to estimate, but 24% of adolescents and 17% of adults under 40 years of age presenting for end-stage care in Australia/New Zealand have RN listed as their primary diagnosis [19]. In the United States, there has been less interest in establishing a specific diagnosis of RN in ESRD patients. When patients – hypertensive or not – are found to have small kidneys by renal ultrasound, further efforts at making a diagnosis are usually abandoned. Most native kidneys are no longer removed for hypertension or in preparation for transplantation. Even if they are, the diseased kidneys are usually not examined carefully – just given an arbitrary diagnosis of end-stage kidney. A North American registry of more than 4000 children and adolescents with ESRD listed the prevalence of RN among these patients at only 4 – 5% [24]. However, the diagnosis submitted for these patients was only a clinical impression because, in most of them, no histopathologic confirmation of the diagnosis was required. In this registry, there was a large group of patients with conditions associated with secondary VUR (obstructive uropathy) and hypoplasia/dysplasia, i.e. small kidneys, some of which may indeed have been injured by VUR or UTI. By comparison, in the first 100 patients < 18 years of age who were transplanted in a single center where histopathologic diagnosis was established in every patient (Table 1), the most common cause for ESRD was RN in 38%; 19% had primary VUR with or without UTI and another 19% had secondary VUR. Similar numbers were reported for ESRD in children from France, Germany and New Zealand [2].

Pregnancy

The incidence of UTI, especially pyelonephritis, during pregnancy was greater in women with renal scarring following UTI in childhood [35]. Moreover, blood pressures were higher in pregnant women with renal scarring than in those with unscarred kidneys. An inverse relationship between maternal blood pressure from any cause and fetal weight has been reported [15]. RN is the basis for pregnancy-induced hypertension in many women, but the correct diagnosis, for one reason or another, is not made very often. It is possible that the blood pressure in most women with RN returns to normal following delivery and after estrogen production has diminished, just as it does in toxemia. Some women with RN will remain hypertensive but asymptomatic post-partum, while others will become markedly hypertensive either with estrogen therapy as part of contraception or during a subsequent pregnancy. A most dramatic deterioration of renal function has been

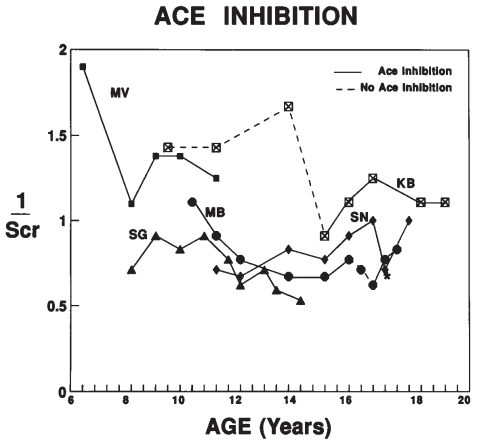

Figure 11. The reciprocal of the serum creatinine concentration (1/Scr) compared to the age of 5 females with bilateral renal scarring, chronic renal insufficiency and hypertension. The broken line (labeled KB) connecting the crossed square symbols represents the treatment period before an ACE inhibitor was available and hypertension was controlled with other drugs. No significant deterioration of renal function over 5 years or more of follow-up observation when hypertension was controlled satisfactorily with an ACE inhibitor.

reported in pregnant women with RN more than 20 years after a febrile UTI [26]. Not only do some of these women become dialysis-dependent during pregnancy, but not all recover following delivery of the fetus and require renal replacement therapy.

Case Presentation

A 16-year-old white female had the diagnosis of RN made when she presented at the age of 11 years with hypertensive encephalopathy (Figure 11, diamond-shaped symbols labeled SN). Renal scarring assessed by IVP was severe bilaterally, and serum creatinine concentration was elevated for age at 1.4 mg/dL (1/serum creatinine = 0.7). The hypertension was managed easily with enalapril 10 mg daily. Over the next 5 years, blood pressure, monitored regularly at home and quarterly by her physician, remained below 110/70 mmHg with no treatment other than enalapril. Renal function improved as evidenced by a gradual decrease in serum creatinine to 1.0 mg/dL even though the patient had increased her lean body mass, completed pubertal development and achieved a normal final adult height by 16 years of age. Despite warnings of the consequences of pregnancy with RN, of hypertension being more difficult to manage when estrogen-containing oral contraceptive agents were taken, and of fetal injury from ACE inhibition therapy, the patient engaged in unprotected sex. After having stable renal function and normal blood pressure for 5 years on the same dose of enalapril, the patient developed a sudden increase in blood pressure to 160/110 mmHg and an increase in serum creatinine to 1.4 mg/dL (decrease in 1/serum creatinine to 0.7). The patient had always been compliant with therapy and even an increase in the enalapril to 20 mg twice daily did not lower the blood pressure. Although denying the possibility of pregnancy, the patient had a positive pregnancy test. By dates and ultrasonography, the pregnancy was estimated at 6 – 8 weeks gestation. The patient chose to abort the fetus and, within 24 hours, her blood pressure was normal. The enalapril dose was reduced again to 10 mg daily and good blood pressure control continued over the next year. Importantly, GFR returned to its antepartum level estimated by a serum creatinine of 1.0 mg/dL. Progesterone-only contraceptive agents were prescribed for the patient without noticeable changes in her blood pressure. The patient was advised that if ever in the future she chose to risk another pregnancy, ACE inhibition therapy must first be discontinued and other antihypertensive agents used to control blood pressure.

ACE inhibitors now carry the warning about their use for treating hypertension, renal disease or heart failure in women of childbearing age. ACE fetopathy has been described as a severe failure of the fetus to develop normally, especially the kidneys, owing, perhaps, to angiotensin being an important growth factor that influences angiogenesis and tissue remodeling. Moreover, the unique hemodynamic changes in the pregnant female, particularly the gradual reduction of blood pressure when PRA and plasma angiotensin levels, indicators of potent vasoconstrictor activity, are increased above normal. When an ACE inhibitor was given during the second and third trimesters of pregnancy, unresponsive hypotension and irreversible renal failure in the newborn infant have been described. Because hypertension in RN is angiotensin-mediated, other antihypertensive agents cannot be expected to give as predictable control of blood pressure as an ACE inhibitor or AT_1 receptor antagonist. Because of the risk of worsened hypertension, ACE fetopathy, and deterioration of GFR – even ESRD – during pregnancy, consideration of a woman with RN becoming pregnant must be a part of the patient's education, but only at the appropriate time when emotional development permits rational decision making.

Progression

There has been no satisfactory explanation to date that characterizes how a kidney, damaged in the past by VUR or pyelonephritis, continues over many years to exhibit parenchymal changes. Newly-identified scars or worsening of established scars usually would suggest further renal injury but not in the absence of VUR, after anatomic or functional obstruction was relieved and when the urine has remained sterile. It is unreasonable to think the progression of renal lesions in RN is due to a prolonged scarring process that takes years to complete – scarring should be completed in months, not years. Acute inflammatory changes in the renal medulla, identical to those associated with IRR and infection, have been identified in scarred kidneys in which VUR had been repaired surgically more than a year before, and the urine was documented to be sterile by frequent cultures for 2 months before nephrectomy [12]. The only difference noted in the lesions found was the paucity of inflammatory cells compared to the ones associated with infection.

One possible explanation for continued scarring in those treated surgically could be that the antireflux procedure itself disturbed ureteral peristalsis. In experimental studies of the canine ureter, re-implantation was associated with reverse peristalsis so that urine flowed retrograde towards the renal pelvis which, instead of VUR, there would be ureteropelvic reflux and, perhaps, IRR. This same phenomenon may occur more proximally when urine from the renal pelvis re-enters the ducts of Bellini, referred to as pyelorenal backflow and observed in micropuncture studies of the rat papilla during progressive saline diuresis. Although most attention to date has been given to the surgical techniques used to correct VUR, no study has been reported on the effect the various procedures have, if any, on normal ureteral physiology.

For lack of a better explanation, and because sterile inflammation has been observed in these kidneys, a immunological mechanism has been proposed as a cause of progressive renal injury. This notion has persisted in spite of the lack of evidence to support it. Perhaps, it is easier to accept at face value because the kidney is injured by so many other immune-mediated diseases. Even a reaction

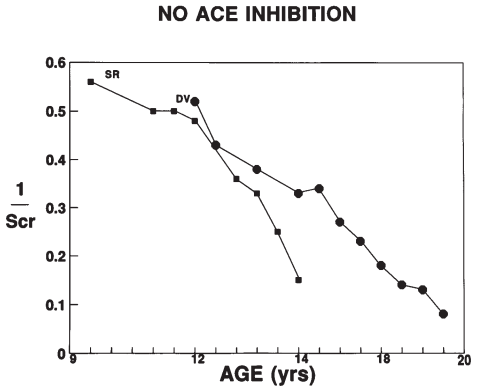

Figure 12. The reciprocal of the serum creatinine concentration (1/Scr) compared to the age of 2 females with bilateral renal scarring, chronic renal insufficiency and hypertension. Progressive deterioration of renal function over 5 – 8 years after VUR corrected, urine remained sterile, and hypertension was controlled satisfactorily with drugs other than an ACE inhibitor.

to Tamm-Horsfall protein has been proposed, but most of these lesions do not contain unusual amounts of PAS positive material.

Consistent blood pressure control at a mean arterial pressure ≤ 100 mmHg, or 125/75 mmHg, is considered essential to slowing the progressive deterioration of renal function in diabetic nephropathy and in primary renal diseases like pyelonephritis. Because many patients with RN are identified because of hypertension, one might argue that the progressive nature of these lesions represent the renal damage caused by uncontrolled hypertension or malignant nephrosclerosis. Media hypertrophy and endothelial proliferation has been identified regularly in the renal vasculature. However, progression has been observed in kidneys never exposed to systemic hypertension as well as those where hypertension has been well-controlled by medication other than ACE inhibitors soon after its onset (Figure 12).

Two findings in kidneys that exhibit deterioration of structure and function may provide evidence for a mechanism to explain the progressive nature of this renal lesion. One finding is compensatory hypertrophy. In RN, the remaining normal parenchyma undergoes marked compensatory changes that may be associated with an actual increase in overall renal dimensions. When this is seen in a child, further normal renal growth may be naively assumed. Compensatory changes allow GFR to remain stable for awhile. By the time GFR has been reduced to 50% of normal, 90% of the functioning renal mass has been destroyed. The other finding is the histopathologic feature of focal glomerulosclerosis – even in unscarred contralateral kidneys – causing some, but not all, to consider this lesion specific for RN. Moderate and heavy proteinuria has been identified in many patients with RN, and is an almost certain sign of eventual ESRD [30]. Most children and adolescents with RN have nothing more than mild proteinuria. Patients with bilateral RN may have increased urinary excretion of microalbumin, retinol-binding protein or N-acetyl-beta-D-glucosaminidase excretion before clinical proteinuria being detected by urinalysis [47]. Whether there is a role for proteinuria to damage renal tubules or cause interstitial inflammation in RN has been mentioned. The glomerular findings described for RN, therefore, appear similar, if not identical, to lesions in remnant kidneys, which may be consequent to hyperfiltration rather than a continuum of injury initiated by IRR in the past. In any event, proteinuria appears to be the hallmark of progressive deterioration of renal function.

ACE inhibition therapy, which does not eliminate intrarenal angiotensin production much more than by half [7], has been shown to reduce proteinuria and to slow the progressive deterioration of renal function in kidneys scarred by pyelonephritis [9]. ACE inhibition

affords a benefit in RN not seen when hypertension is treated successfully with other antihypertensive drugs [23]. Progressive changes in renal function in young hypertensive females with RN are depicted in Figure 12 by serial ratio of 1/serum creatinine over 5 years or longer. Those 2 patients whose blood pressure was controlled effectively with drugs available before the introduction of ACE inhibitors (propranalol and hydralazine) exhibited progressive deterioration of GFR; both were treated first by dialysis, then received a renal allograft. By comparison, the girls treated first with captopril and later with enalapril had their blood pressures controlled as well, but exhibited little change in GFR. The criticism of using 1/serum creatinine in children is acknowledged, but these girls were of similar ages when the diagnosis of RN with hypertension was made. Moreover, all had severe scarring of both kidneys with similar elevations of systolic pressure to > 180 mm Hg and of diastolic pressure to > 120 mm Hg before treatment. This benefit of ACE inhibition may extend as well to normotensive patients with RN and other progressive renal diseases.

The protection afforded the damaged kidney by ACE inhibition is not mediated solely through control of blood pressure [23]. The production of angiotensin in the intrarenal circulation and tubules has been shown to be approximately 1000 fold greater than in the systemic circulation [41]. Similarly, the renal metabolism of angiotensin was demonstrated to be as efficient as its synthesis. A disturbance either in the production of angiotensin or its metabolism could cause localized renal ischemia, perhaps, by intense vasoconstriction of glomerular or post-glomerular blood vessels. angiotensin is also known as a growth factor important in angiogenesis, tissue remodeling after injury and hypertrophy of smooth muscle. Moreover, it may promote fibroblastic activity not only to facilitate the repair of injured tissue but also to cause scarring – even progressive fibrosis. Therefore, many of the consequences attributed once to IRR or infection may, in fact, be explained better by a localized increased production of angiotensin in the repair of damaged tissue. Once initiated, either the further production of angiotensin or a failure of its intrarenal metabolism may promote compensatory responses at first, then cause hyperfiltration and ischemic injury resulting in progressive reduction in renal size – simulating progressive scarring, with gradual deterioration in overall renal function. Perhaps even more aggressive efforts to control angiotensin, say with higher doses of ACE inhibitors and angiotensin receptor blockade, or both may afford even better control of remnant kidneys, not only in RN, but also other renal diseases characterized by progressive deterioration of structure and function.

Dietary protein intake has been shown in renal ablation models and in various renal diseases, both diabetic and non-diabetic, to have an adverse effect on kidney function. While conclusive evidence for any clinical benefit of a protein-restricted diet in retarding or preventing progression altogether of renal disease in humans has not been demonstrated to date, there is enough information to suggest a role for reducing protein intake in most patients with chronic renal disease, even when renal functional impairment is mild or moderate. When combined with other measures such as control of hypertension and inhibition of angiotensin, the ADA recommended normal protein intake each day for adolescents and young adults of 1 g/kg body weight is considerably less than the usual protein intake for most people living in North America, and may be beneficial in overall efforts to preserve renal function.

Strategies for Prevention

RN is one of very few kidney diseases with the immediate potential of not just being modified, but actually prevented. Although there is a potential risk for renal injury from acute pyelonephritis at any age, most scarring which leads to chronic renal insufficiency seems to originate in infancy and early childhood when the kidney appears more vulnerable to insult, when symptoms of UTI may be overlooked or mistaken, and when appropriate treatment may not be instituted promptly. Whether a patient has pyelonephritis or only cystitis at the time of an acute illness is an academic discussion for a later time. Also, the debate about whether to treat asymptomatic bacteriuria should not enter into any decision of a febrile child, especially if the child is known to have VUR.

Firstly, the clinical suspicion of acute pyelonephritis at any age must be confirmed by urine culture; urinalysis never serves more than a screening role either in diagnosis of the first UTI or during follow-up of children with a prior UTI. Even the most experienced clinician – using reagent strips for leukocyte esterase and nitrite, semi-quantitative urine white blood cells estimates, Gram stains of uncentrifuged urine, C-reactive protein measurements or erythrocyte sedimentation rates (ESR) – cannot be relied upon to discern the clinical differences. The urine culture is the gold standard for establishing the diagnosis of UTI regardless of the patient's age. All the other laboratory tests may improve clinical suspicion of UTI before the preliminary results of the urine culture are known, but, in reality, only increase the cost of making the diagnosis. Acute renal inflammatory lesions by DMSA renal scans have been described in some patients thought at first to have only cystitis.

Therapeutic intervention, however, does not have to be delayed for a urine culture report. Antibiotic treatment should be instituted immediately after the clinical diagnosis is suspected and the urine culture obtained. Where patient or parent non-compliance may be anticipated, parenteral antibiotic therapy should be considered. No antibiotic will be effective against every urinary pathogen, therefore the drug initially prescribed may need to be changed when the sensitivities of the organism are known or the urine obtained for culture after 48 hours of treatment is not yet sterile. The duration of treatment is somewhat arbitrary. In the uncomplicated urinary tract, 1 – 3 days of oral or parenteral treatment with an appropriate antibiotic has been shown to be sufficient. Failure of an abbreviated course of antibiotic therapy has been associated with a high incidence of urinary tract abnormality. Seven to 10 days of antibiotic treatment is more conventional, even though there are no studies to confirm any additional benefit. The treatment should continue, at least in a prophylactic regimen, until the decision is made for instrumenting the bladder for VCUG in those children who have not previously undergone radiologic investigation. More importantly, the urine should still be sterile a week after discontinuing treatment of any duration. The goal of the clinical follow-up is to assure, as best one can, that the urine remains sterile. Even under the most compliant circumstances, breakthrough UTI can be expected in a third of patients who have VUR. The best clinical outcomes have been reported in an uncontrolled trial with long-term daily antibiotic prophylaxis where new scars in patients with VUR were detected in only about 2% of patients – these were considered non-compliant with therapy [46]. By comparison, new scars were observed in up to 21% of patients with VUR treated acutely as each new UTI was recognized [32].

There is a clinical notion that has gained popularity in recent years that renal scarring in patients with VUR cannot be prevented. In other words, because most patients with renal scarring already have it when first evaluated for UTI and most of these patients are identified in the first 5 years of life, this pessimistic viewpoint holds that preventing renal damage is not possible. Evidence to the contrary includes new scars observed to develop in older children, adolescents and adults with previously normal kidneys or in locations within the kidney of acute lesions of pyelonephritis identified by DMSA technology that progress to scarring. Finally, in Sweden, where the management of UTI in children has been a priority in a socialized system with good access to medical care and follow-up, the incidence of renal scarring in patients with VUR has been reduced significantly – compared to results reported 25 years ago – to what is probably the lowest reported incidence in the world today, about 10%. This clinical evidence supports experimental observations in which renal scarring in animals was avoided when appropriate antibiotic therapy was initiated within 5 days of pyelonephritis being induced.

Patients at risk of renal scarring must be identified early and, if possible, before the first UTI ever develops. Screening programs are not recommended because the yield of pathology in asymptomatic children is < 0.5%. There are 2 situations in which screening patients at risk of renal scarring has merit. The first is the newborn infant whose dilated urinary tract was noted by fetal ultrasound examination. While the kidney may have sustained injury before birth, it would be secondary to VUR alone because fetal urine is sterile. Most of these infants will develop UTI within the first week of postnatal life, which permits pyelonephritis to develop in kidneys already damaged, perhaps, by VUR or obstruction. Any protection afforded these infants by prophylactic antibiotic treatment from birth seems warranted at least until the urinary tract can be investigated. The other group of children at risk of renal injury from UTI associated with VUR are siblings of patients with VUR. It is generally agreed, at present, that all siblings < 5 years of age should have a screening VCUG performed. This age limit has been set arbitrarily. The incidence of VUR in asymptomatic siblings decreases with age – just as it does in those with UTI – but may still be identified in children older than 5 years. VUR-associated renal injury which is manifested in successive generations may be enough reason to ignore the factor of age to assure each family member at risk is identified and protected as early as possible. Each newborn sibling of patients with VUR should be placed on antibiotic prophylaxis until the VCUG can be scheduled. While this practice may seem overly aggressive to some, it is a very conservative attitude for those who have observed a normal kidney damaged irreversibly by a single episode of pyelonephritis (Figure 3).

There will be no progress in reducing the incidence of RN without education. Clinicians who treat children must understand their unique problems associated with UTI and provide consistent treatment, evaluation and surveillance of patients with UTI through young adult life. Then, treating or consulting physicians must educate the patient or parents as to the importance of being compliant with treatment and the consequences that may be expected to follow even a single episode of UTI in a child. Finally, society, in general, needs to become aware of the morbidity associated with UTI. Because cystitis is common among sexually-active women – who often are mothers, the almost casual approach by physicians to the diagnosis and treatment of their bladder infections, conveys the message

that UTI in their children, their nieces and nephews and their neighbors' children can be treated casually as well.

Conclusion

Even as late as 1950, the only antibacterial agents available to treat acute pyelonephritis were sulfa compounds and streptomycin. Moreover, the treatment of usually severe, sometimes malignant hypertension associated with chronic atrophic pyelonephritis was limited to barbiturates and reserpine as recently as 1965. Therefore, a cardiorenal complication of pyelonephritis proved fatal for many individuals in the past and will continue to do so even today.

Unfortunately, the pendulum may be swinging away from a more aggressive pursuit of UTI, at least in children. The greatest clinical discouragement comes from very little progress being made over the past 30 years in our understanding of the pathophysiologic mechanisms in RN. The bulk of the medical literature to date represents, with few exceptions, case reports and experience with various surgical techniques rather than well designed, controlled clinical trials. The clinician treating the first UTI in a child does not always appreciate the potential risk of the infection, and is not the one who will provide the medical care later in life when the patient develops hypertension, heart disease, stroke or chronic renal insufficiency. In the absence of a much more consistent clinical care path, including long-term outcome measures, renal injury from pyelonephritis is unlikely to be eliminated entirely.

If pyelonephritis can be detected early in its course, treated effectively and further episodes of UTI prevented, the incidence of renal scarring may be reduced significantly. Moreover, if the patient with renal scarring is monitored closely to detect hypertension that is then treated effectively with an effective inhibitor of angiotensin, the complications attributable to systemic hypertension itself can be avoided. Once chronic renal insufficiency has developed, further deterioration of renal function in RN may be modified by dietary protein restriction and by inhibiting angiotensin – even in normotensive patients. Preliminary clinical data provide hope that development of ESRD in patients with RN can be delayed – if not avoided altogether. It is not yet time to accept defeat in our pursuit of understanding the mechanisms of renal injury from VUR-associated pyelonephritis. Too many patients are still at risk.

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Urinary Tract Obstruction

Thomas H. Waid

Obstruction of the urinary tract is a condition that physicians in all disciplines frequently encounter. Regardless of the cause, obstruction of urinary outflow leads to renal impairment that is initially reversible if obstruction is alleviated. The tubules are primarily affected; however, with time, progression results in parenchymal atrophy with glomerular sparing until late in the clinical course. Long-standing obstruction affects the kidney grossly as well as microscopically, resulting in dilatation of the pelvis and calices and thinning of the cortex. Whether the obstruction is unilateral or bilateral, acute or chronic, it produces changes in the anatomy and physiology of the kidney involved.

Therapeutic efforts are often aimed solely at relieving the cause of obstruction. Therefore, the sequelae of obstruction and its management may be overlooked. Often a significant salt-and-water diuresis, known as post-obstructive diuresis (POD), results and the physician's thought process must shift from relieving and perhaps treating the obstructing lesion to treating the physiologic derangements associated with the POD.

Nephrologists, urologists, and internists should have a working knowledge of the renal response to obstruction and its alleviation. This chapter encompasses diagnoses, pathophysiology, and treatment of obstruction and management of POD.

Incidence

Impairment of normal urine flow by functional or structural changes in the urinary tract is a common occurrence in all ages. Pyelocaliectasis has been found on autopsy of 3.5% of adults with a 1 : 1 male to female ratio. Additionally, 2% of children display hydronephrosis at autopsy, mostly because of congenital anomalies. After age 60, obstruction occurs more often in males, resulting from benign prostatic hypertrophy and prostatic cancer, whereas middle-aged women develop obstructive uropathy as a result of pelvic cancer or retroperitoneal fibrosis. Currently in the United States, the incidence of patient visits attributed to obstructive uropathy is about 380 out of 100,000 patient visits.

Causes of Partial or Complete Urinary Obstruction

Obstruction of the urinary tract can occur at any level and has many causes [1, 2]. Furthermore, obstruction can be complete, implying obstruction of all functioning nephrons, or partial. In the former scenario, obstruction is

Table 1. Causes of Urinary Tract Obstruction

Kidney
- Urolithiasis – pelvis
- Ureteropelvic junction obstruction
- Papillary necrosis
- Tumor (malignant or benign)
- Intratubular obstruction (crystalline nephropathy)

Ureter
- Tumor (papilloma, transitional cell carcinoma)
- Urolithiasis
- Congenital obstructive megaureter
- Eagle Barrett syndrome (prune belly)
- Ureterocele, orthotopic or ectopic
- Ectopic ureter
- Retrocaval ureter
- Retroperitoneal fibrosis (idiopathic, drugs, irradiation)
- Inflammatory bowel disease
- Metastatic tumor, retroperitoneal adenopathy
- Infection (tuberculosis, *Schistosoma haematobium*, fungus ball)
- Ureteral valve
- Ureteral polyp
- Pelvic lipomatosis
- Lymphocele

Bladder
- Neurogenic bladder (spinal cord defect, trauma, diabetes, multiple sclerosis, Parkinson's disease,
- strokes)
- Bladder neck contracture
- Transitional cell carcinoma
- Hemorrhagic cystitis
- Blood clots
- Infection (pyocystis, schistosomiasis)
- Detrusor, sphincter dyssynergia
- Bladder stones

Urethra
- Stricture
- Detrusor-sphincter dyssynergia
- Trauma/obliteration
- Meatal stenosis
- Posterior and anterior urethral valves
- Prostatic hypertrophy or cancer
- Calculus
- Polyp or urethral carcinoma
- Phymosis, paraphymosis
- Diverticulum

Table 1. Causes of Urinary Tract Obstruction (Part 2)

Extrinsic compression
- Cervical tumor
- Uterine tumor or pregnancy
- Endometrial tumor
- Endometriosis
- Uterine prolapse
- Vaginal distension
- Aneurysms
- Aberrant crossing vessels
- Abscess
- Gartner's duct cyst
- Crohn's disease
- Diverticulitis

bilateral or involves an anatomically or functionally solitary kidney. The causes of complete or partial obstruction are listed in Table 1.

Intratubular obstruction is the result of crystalline nephropathy and cannot be demonstrated radiographically or sonographically. In many cases, such as in tumor lysis syndrome, sulfa drug administration, or ethylene glycol poisoning, there will be crystals in the urinary sediment (uric acid, sulfa, oxalate, etc.) that yield a timely diagnosis. Because the crystal deposits are the result of filtration from the blood and crystallization in the lumen of all nephrons of the kidney, the obstruction is, by definition, bilateral and complete.

Obstruction of the renal calix or pelvis may be unilateral or bilateral, complete or partial. Unilateral obstruction may result in ipsilateral loin pain, microhematuria, gross hematuria, or it may be asymptomatic. However, there will be little or no change in blood urea nitrogen (BUN), creatinine, or electrolytes if the unobstructed kidney is functioning normally. Causes of obstruction in the pelvis or calices include renal stones of any type, including staghorn calculi, renal papilla sloughed during papillary necrosis, and benign and malignant tumors.

Ureteric obstruction can be unilateral or bilateral, partial or complete. Ureteral colic and flank pain result from acute obstruction and may be accompanied by nausea, vomiting, scrotal pain and micturitional urgency; however, chronic indolent obstruction may be asymptomatic.

Malignant tumors such as transitional cell carcinoma, stones, and retroperitoneal lymphadenopathy constitute the more common causes of ureteral obstruction. Ureteric strictures may be caused by multiple stone passage, instrumentation or a previous operation, pelvic irradiation, infections such as renal tuberculosis or *Schistosoma haematobium* infection, and inflammatory bowel disease. Additionally, in cases of inflammatory bowel disease, radiation, and penetrating trauma, a urinary fistula can develop from the ureter or bladder with resorption of urine by the peritoneal membrane and resultant elevation in BUN, creatinine, chloride, and other electrolytes. This urinary resorption may mimic obstruction, although no obstruction exists per se.

Extrinsic causes of ureteral obstruction are best classified by the system of origin. Most extrinsic lesions obstructing the ureters originate in the reproductive system, including pregnancy and cervical, endometrial, and ovarian cancer as well as uterine prolapse and endometriosis. Vascular abnormalities such as aortic or iliac aneurysms or aberrant vessels and retroperitoneal lymphadenopathy from malignancy cause extrinsic obstruction. As previously stated, inflammatory bowel disease, particularly Crohn's disease, can cause strictures and fistulas of the ureters and bladder, respectively. Finally, retroperitoneal fibrosis results in encasement of the ureters, inhibiting peristalsis and causing significant partial obstruction. Patients usually present with vague back pain and an elevated erythrocyte sedimentation rate (ESR), BUN, and creatinine. There may also be a history of methyldopa, methysergide, or beta blocker drug use or retroperitoneal malignancy requiring chemotherapy or irradiation. Unlike other causes of obstruction, hydronephrosis may not be apparent radiographically or sonographically because of fibrous encasement of the upper urinary tract.

Pathophysiology of Obstruction

Obstruction of the urinary tract generally causes dilatation of all portions of the urinary tract proximal to the level of obstruction ascending to the renal parenchyma. The initial response is one of muscular hypertrophy of the proximal ureter and renal pelvis followed by production of collagen and elastic tissue. The latter connective tissue impairs myogenic impulse transmission, thereby disturbing peristalsis [3, 4]. Hydronephrosis causes tubular dilatation and tubule cell atrophy, appearing within 7 days of obstruction in the distal tubule and within 14 days in the proximal tubule. By day 28, approximately 50% of the medulla is lost, and there is obvious cortical atrophy because of the associated loss of proximal tubules. Glomerular changes occur only after 28 days of obstruction. Although there is an eventual reduction of blood flow in hydronephrosis, it appears to be the result of impaired venous drainage and not only to an alteration in arterial flow [5, 6, 7].

When complete obstruction occurs, the urine in the obstructed kidney is not static; rather, there is a turnover of urine in hydronephrosis as most urine extravasates via the calyceal fornix. Urine can exit the renal pelvis by extravasation, pyelolymphatic back-

flow, and pyelovenous backflow while glomerular filtrate replenishes the urine and maintains the hydronephrosis. With lower pressure, the urine exits into the lymphatics; with higher pressure, the renal venous system resorbs the urine [8, 9]. In chronic obstruction of 6 to 34 days' duration, the quantity of urine escaping the renal pelvis ranges from 0.04 to 0.16 mL/min. Glomerular filtration in complete obstruction is 1.2 mL/min after 2 weeks and 0.4 mL/min after 5 weeks [10].

Renal Compensation for Obstruction

When a single kidney fails, regardless of the etiology, there is adaptation within the remaining kidney to restore total renal function toward normalcy. Such adaptation occurs both by hypertrophy and hyperplasia [11]. As a result of unilateral obstruction, there is an ipsilateral and contralateral increase in renal mass in the first week. Thereafter, there is progressive hypertrophy in the nonobstructed kidney while the obstructed kidney slowly atrophies [12, 13]. During this compensatory hypertrophy, the glomeruli increase in size but not in number. Perhaps this is the result of single nephron hyperfiltration.

Upon alleviation of obstruction, the obstructed kidney regains some function, and although compensatory hypertrophy of the contralateral kidney persists, total renal function does not recover to normal by 4 months. The degree of recovery of renal function after relief of obstruction varies with the duration of obstruction and the severity of pyelolymphatic or pyelovenous backflow of urine [14]. Upon releasing total ureteral obstruction of 4 weeks' duration, the glomerular filtration rate (GFR) returns to 35% of normal by 5 months; however, there is no recovery of function after 6 weeks of total ureteral obstruction.

Hydrostatic Pressures in the Ureter, Pelvis, and Renal Tubules During Obstruction

Normally the pressure in the renal pelvis is between 6 and 7 mm Hg, exceeding intraperitoneal pressure and that within the bladder and ureter. The pressure in the normal proximal tubule is 14 mm Hg, and the pressure from glomerular filtration (glomerular capillary pressure [60 mm Hg], less capillary oncotic pressure [25 to 30 mm Hg], less the hydrostatic pressure in Bowman's space [15 mm Hg]) is between 15 and 20 mm Hg [15].

During urinary tract obstruction, renal pelvis and ureteral pressures rise acutely only to decline to 50% of the peak value within 24 hours. Over the next 2 months, the intraureteric pressure steadily decreases to a nadir of 15 mm Hg [14, 16]. This higher ureteral pressure, sometimes measured at 50 – 70 mm Hg during acute obstruction, results from filtration pressure and active muscle contractions in the renal pelvis and ureter [15, 17]. Administration of mannitol or volume expansion with saline can increase ureteral pressures to 100 mm Hg [18, 19]. Proximal tubular pressures may acutely rise to 40 mm Hg; however, within 24 hours the proximal tubular pressure is below normal because of afferent renal arteriolar vasoconstriction [20, 21].

Glomerular Filtration, Renal Blood Flow, and Tubular Function in Acute Obstruction

Glomerular filtration and renal blood flow (RBF) are affected as a consequence of afferent renal arteriolar constriction. As proximal tubular pressure increases, the GFR falls because of afferent renal arteriolar vasoconstriction beginning within 5 hours of the onset of

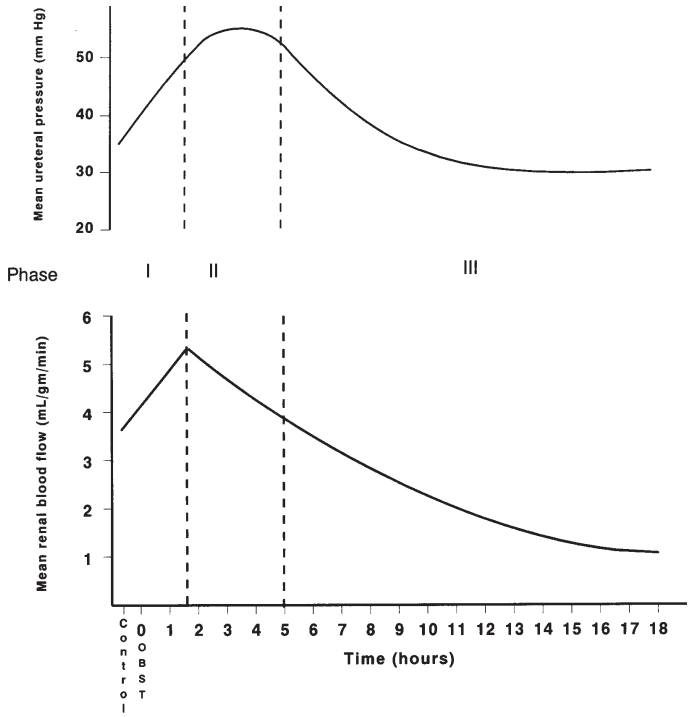

Figure 1. The triphasic response of ureteral pressure and renal blood flow in response to unilateral obstruction. Adapted from [Vaughan ED Jr, Bruce RG, Waid TH, Lucas BA et al 1997 Understanding postobstructive diuresis. Contemp Urol 9: 53-66] with permission.

obstruction. Additionally, as the proximal tubular pressure rises, there is a declining pressure gradient between the glomerulus and the proximal tubule. GFR is 52% of normal 4 hours after the onset of complete obstruction but only 2% of normal after 48 hours [22]. Additionally, during the first 24 hours of obstruction, RBF and ureteral pressure in the ipsilateral kidney display a triphasic relationship (Figure 1) [16, 23]. In the first 90 minutes, there is an increase in RBF and ureteral pressure consistent with preglomerular vasodilatation, a phenomenon that is prostaglandin mediated [24]. The increase in RBF appears to be confined to the cortex with the majority being distributed to the inner cortex [25].

The second phase occurs from 90 minutes to 5 hours after acute obstruction and is the result of preglomerular arteriolar resistance. The mean RBF begins to decline; however, the mean ureteral pressure continues to rise and then plateau. The third phase then ensues from 5 – 18 hours, marked by declines in both ureteral pressure and RBF. The presumed mechanism would appear to be persistent preglomerular vasoconstriction, but the exact mechanism remains unknown [26].

Tubular function is altered in partial acute ureteral obstruction because of a slower rate of tubular fluid flow. As a result, urine volume decreases, osmolality increases, and urinary sodium concentration may be reduced [27]. After complete acute ureteral obstruction, there is a further decline in GFR, and tubular function becomes impaired, which results in a temporary concentrating defect after the release of acute ureteral obstruction [28].

The effects of partial and complete chronic obstruction have also been studied. In chronic partial obstruction, there is a reduction in RBF, GFR, urinary concentrating ability, so-

dium reabsorption, and urinary acidification (hydrogen ion excretion) [27, 29]. Indeed, impairment of urinary acidification is a result of impairment in all aspects of tubular hydrogen ion handling, including ammonia excretion, titratable acidity, and bicarbonate reabsorption [30]. Complete chronic obstruction displays a decline in ureteral pressures after 24 hours, and the decline continues over 6 – 8 weeks. Proximal tubular pressures may normalize or become 30% lower than normal [26, 31]. Because of afferent arteriolar vasoconstriction, RBF progressively declines to 70% of normal at 24 hours and 50%, 30%, and 12% at 3, 6, and 50 days, respectively [16, 23]. The most significant reductions in RBF are seen in the outer renal cortex and the inner medulla [25, 32].

As stated, the rate of glomerular filtration declines progressively in chronic complete obstruction, with fluid exiting the collecting system by pyelolymphatic, pyelovenous, and pyelotubular backflow. The GFR is 0.4 mL/min at 5 weeks of obstruction; however, this is enough to replace the exiting tubular fluid [10]. One week after release of complete obstruction of 2 weeks' duration, the GFR is restored to 15% of normal with the maximum attainable recovery being 46% of normal. No recovery of GFR is ever noted after 6 weeks of chronic obstruction [33].

Complete urinary obstruction impairs all tubular function except urinary dilution, and upon release of obstruction, urinary concentrating ability and sodium conservation are severely impaired. Although urinary concentrating ability can be recovered after release of 2 weeks of complete obstruction, it remains permanently impaired after 4 weeks of obstruction [14]. Other tubular functions are likewise impaired, including glucose transport, potassium excretion, sodium resorption, and urinary acidification. Inability to concentrate urine remains the primary defect [14, 34].

Obstruction and Hypertension

Hypertension may be associated with either unilateral or bilateral obstruction. Acute unilateral obstruction is associated with renin elaboration and renin-dependent hypertension [14, 23]. Chronic unilateral obstruction may be associated with hypertension. However, renin is rarely elevated in bilateral obstruction, and patients usually have volume-dependent hypertension in this setting.

Clinical Presentation and Diagnosis of Obstruction

The clinical manifestations of urinary tract obstruction vary, depending on the location, duration, and degree of obstruction. Patients with complete bilateral obstruction or with an obstructed solitary kidney may present with acute oligoanuric renal failure, whereas partial obstruction of both kidneys or a solitary kidney may result in chronic azotemia with polyuria or urine output alternating from oliguria to polyuria. Pain is more likely to be associated with acute obstruction; however, obstruction may be totally asymptomatic and occur without laboratory findings or clinical manifestations [35].

As stated previously, hypertension may occur as a consequence of obstruction and may be volume or renin dependent. Polycythemia because of erythropoietin secretion has been described; however, in severely azotemic patients a normochromic, normocytic anemia is more commonly seen. Physical examination may uncover a palpable flank mass or bladder, and rectal or pelvic examination may reveal an enlarged prostate gland or gynecologic pathology. In thin patients, bladder masses may

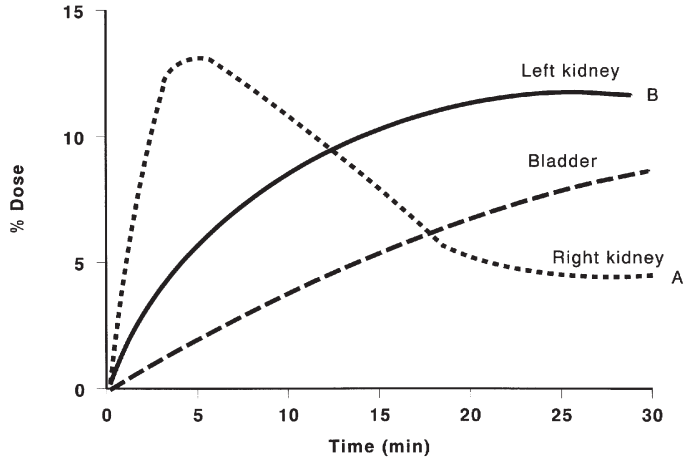

Figure 2. Renogram showing unobstructed pattern in the right kidney (A) and an obstructed pattern in the left kidney (B). Appearance of radionuclide in the bladder is seen in the bladder curve.

be palpated bimanually. Finally, assessment of volume status is very important in determining how to best manage the patient. Complete obstruction usually results in volume expansion, which in severe cases can produce congestive heart failure (CHF) and pulmonary edema. Volume depletion can occur in unilateral obstruction in which the contralateral kidney excretes salt and water in a compensatory fashion.

Laboratory evaluation may or may not be helpful. The diagnosis can be aided by the presence of azotemia, a normal anion gap (8 – 12 mmol/L), hyperchloremic metabolic acidosis with normal potassium, or hyperkalemia. The urinalysis will usually have a pH of > 5.5 on a fresh specimen. The urinary sodium will be ≥ 40 mmol/L and the fractional excretion of filtered sodium (FENa) will be > 1. First voided morning urine will reveal the patient's lack of concentrating ability with a low specific gravity (1.002 to 1.010) and osmolality ≤ 400 mOsm/kg. If renal failure is far advanced, the patient may develop a uremic metabolic acidosis in which the anion gap will be elevated. Urinary sediment can range from bland to active including erythrocytes (due to tumor, BPH, clots, or stones), infection; leukocytes (due to infection, or stones), or crystals (due to stones, infection, or crystalline nephropathy) [35]. Finally, hypernatremia may occur if patients are partially obstructed and sustain severe water losses because of tubular insensitivity to antidiuretic hormone (ADH), i.e. nephrogenic diabetes insipidus.

Ultrasonography remains the most useful test in diagnosing urinary tract obstruction. It is noninvasive, relatively inexpensive, and both sensitive and specific. Sonography will rarely yield a false-positive result because of anatomic variations of the pyelocaliceal system that may be misinterpreted as hydronephrosis. Sonography may provide false-negative results in patients who are both obstructed and volume depleted or in patients obstructed because retroperitoneal fibrosis has encased the entire collecting system. In the latter case, retrograde pyelography with drainage films, placement of ureteral catheters or stents, or placement of percutaneous nephrostomies and antegrade nephrostograms may diagnose and treat the obstruction.

Radioisotope renography can be useful in diagnosing urinary tract obstruction and differentiating between mechanical (anatomic) obstruction and functional (aperistaltic) obstruction (Figure 2). Isotope scanning is unique in the investigation of obstruction be-

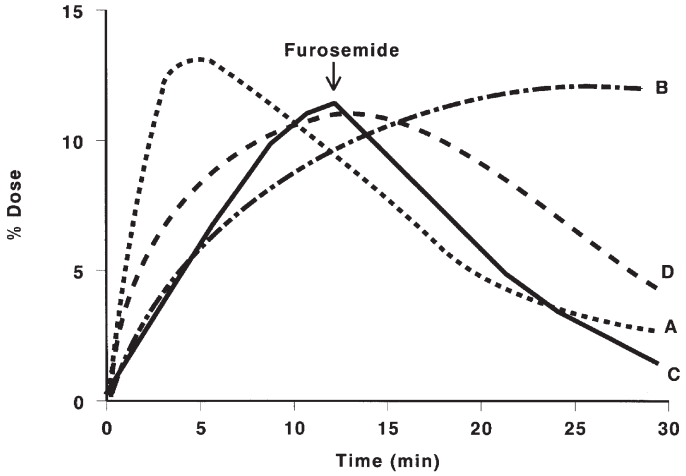

Figure 3. The diuretic renogram. Results are followed on a time activity curve with a normal curve excluding obstruction (A). A rising curve unaffected by diuretic administration indicates obstruction (B). Response to diuretics suggests a dilated collecting system, which is not obstructed (C). A partial diuretic response indicates subtotal obstruction (D).

cause it offers simultaneous quantification of renal function and dynamic analysis of urine flow rates. Urinary tract dilitation without a demonstrable anatomic lesion may occur in ureteric reimplantation, pyeloplasty, ureterolithotomy, pyelolithotomy, primary megaureter or vesicoureteral reflux. If a standard renogram is abnormal with no or sluggish elimination of radionuclide tracer at 10 – 30 min, furosemide is given intravenously (IV) while the study continues. One of 4 responses may occur (Figure 3):

- The renogram is normal, excluding obstruction (A).
- The renogram curve remains obstructive, confirming anatomic obstruction (B).
- The obstructive curve is converted to a nonobstructive curve with rapid and complete elimination of the tracer (C).
- The obstructive curve displays a partial response to diuresis, indicating subtotal or partial obstruction (D).

It must be noted that in patients with abnormal voiding or in patients with free vesicoureteral reflux, the bladder must be drained with a catheter or the test result may suggest mechanical obstruction, when, in fact, it is not present. A repeat scan with a Foley catheter in place is then warranted.

Finally, perfusion-pressure flow studies can be obtained to rule out obstruction. Also known as the Whitaker test, the procedure measures the perfusion pressure of a solution passing antegrade through a percutaneous nephrostomy tube at 10 mL/min. A pressure rise of ≥ 22 cm water indicates obstruction, whereas a rise of < 15 cm of water excludes obstruction. Values ranging between 15 and 22 cm water are said to be equivocal [36, 37]. The major disadvantage of the test is its invasiveness. The results of numerous studies comparing perfusion pressure flow with the less invasive diuretic isotope renography have been variable, with correlations ranging from 53 – 86% [37, 38]. Additionally, studies comparing diuretic renography with renal pelvic morphology appear to correlate well (r = 0.88) [39].

Summary of Physiologic Conditions During and After Release of Obstruction

Changes in renal physiology depend on whether ureteral obstruction is partial or complete. Complete obstruction often results in the uremic state because of retention of waste products normally excreted. Anatomically the tubules look normal in complete obstruction, whereas in partial obstruction, the tubules of the nonobstructed kidney are collapsed and the nephrons are poorly perfused. Pressures are elevated in the proximal and distal tubules in complete obstruction but are lower than normal in the unobstructed units in partial obstruction. Afferent arterial pressure is elevated in complete obstruction and diminished in the unobstructed units in partial obstruction.

RFB and GFR are reduced to one-third of normal in both complete and partial obstruction, in the former by increased proximal tubular pressure and in the latter by afferent arteriole vasoconstriction of the unaffected kidney. When complete obstruction is alleviated, the tubular pressures normalize; however, the GFR diminishes because of afferent arteriolar vasoconstriction. Urine flow may be increased dramatically after the release of complete obstruction, and the excretion of urea, potassium, phosphate, and magnesium is enhanced. A diuresis occurs regardless of fluid balance until the GFR can restore sodium delivery to the tubules and medullary hypertonicity can be regained. The urinary concentrating defect persists for several days beyond the salt-wasting defect, and the ability to conserve urinary sodium should herald the recovery of concentrating ability and attenuation of the diuresis.

After the release of partial obstruction, the affected kidney has a normal urine flow of dilute urine because of reduced GFR and RBF and impaired concentrating ability. The contralateral kidney maintains homeostasis and a POD is often clinically inapparent.

Mechanisms of POD

POD occurs when there is correction of complete bilateral obstruction or complete obstruction of a solitary functioning kidney. During unilateral obstruction, urinary and serum abnormalities are obscured by the unobstructed kidney and POD rarely occurs. First characterized as a syndrome of volume and electrolyte imbalance following relief of obstruction by catheterization, POD involves the production of large volumes of urine immediately after the relief of urinary obstruction [40]. This syndrome occurs when all nephrons are obstructed and patients still have reversible, albeit advanced, renal failure. Three mechanisms are postulated (Figure 4): a defect in urinary concentrating ability, impaired renal sodium reabsorption, and solute diuresis due to retained urea or iatrogenic administration of sodium-containing IV fluids [41].

Upon relief of complete urinary tract obstruction, RBF and GFR initially decrease as a result of the action of renal prostaglandins [42]. Because a defect in urinary concentration and sodium conservation exists, diuresis ensues. When the diuresis is prolonged and severe, significant loss of water, sodium, potassium, and magnesium can result in hypovolemia and electrolyte abnormalities that

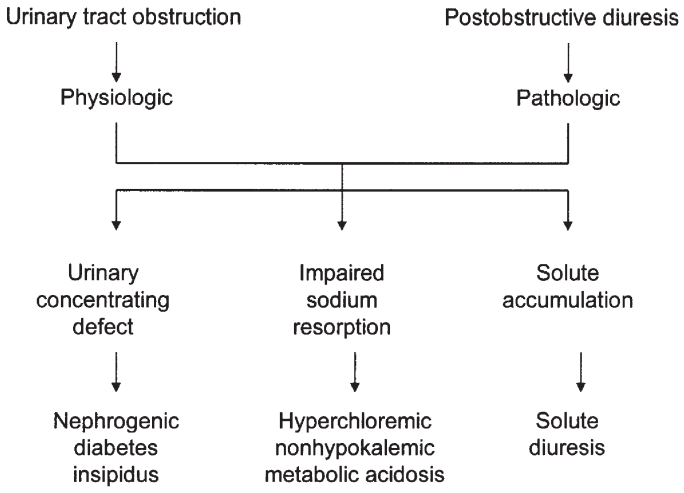

Figure 4. Pathophysiologic alterations in urinary tract obstruction and postobstructive diuresis. These mechanisms are physiologic during obstruction, continue pathologically in the postobstructive period until the hypertonicity of the renal medulla is restored. Solute accumulation and diuresis are pathologic when IV fluids are inappropriately administered. [Bruce RG, Waid TH, Lucas BA 1997 Understanding postobstructive diuresis. Contemp Urol 9:53-66] with permission.

cannot be adequately prevented or restored by oral intake of solute (diet) and water [34].

Patients with prolonged POD are insensitive to the administration of ADH or deoxycorticosterone acetate (DOCA), which explains the 2 patterns of diuresis seen in POD. The more common clinical entity is the diabetes insipidus-like nephropathy, which is usually associated with chronic obstruction and is a self-limiting concentrating defect leading to free water losses. Postobstructive sodium-losing nephropathy is rare but is a more severe and protracted diuresis that occurs in the setting of severe bilateral obstruction and reversible renal failure [43]. The question becomes how and to what degree do urinary concentrating defects and renal sodium loss contribute to pathologic water and electrolyte loss in POD.

As stated earlier, the urinary concentrating defect is the result of altered renal hemodynamics in the early phases of complete obstruction. The GFR initially decreases after obstruction is relieved, and without tubular solute, including sodium and urea, the medullary tonicity cannot be maintained. Until glomerular flow and filtration improve and provide solute to restore the medullary tonicity, hypotonic urine losses will continue. Clinically, this generally results in a water diuresis of 1 – 4 days' duration.

The natriuresis occurring in POD results from increased delivery of sodium to the distal tubule in the face of limited capacity of the distal tubule to resorb the increased sodium load [44]. This state is not unlike that produced by loop diuretics, which, when administered, block chloride and sodium resorption in the loop of Henle, increase delivery to the distal tubule, and thereby create a solute-rich urine. Additionally, disturbances in proximal sodium resorption can occur due to proximal tubular dysfunction and further add to distal tubule solute delivery. The naturesis of POD is therefore not only related to enhanced sodium excretion to relieve volume expansion, but also to a pathologic decrease in tubular sodium reabsorption [44].

Patients with POD have elevated serum levels of atrial natriuretic factor (ANF) [45]. ANF is elevated whenever there is extracellular volume expansion, whether acute or chronic, and has four effects: natriuresis, diuresis, vascular relaxation, and increasing GFR via afferent arteriole dilation and effer-

ent arteriole constriction [46]. ANF has been associated with complete urinary obstruction and to the development and control of POD [47].

Diagnosing and Treating POD

The diagnosis of POD should be considered whenever excessive diuresis occurs after obstruction is alleviated. Recognition of the patients at greatest risk for developing POD is an important first step. Complete urinary tract obstruction is usually the predisposing clinical condition. The clinical situation is often encountered in elderly males with bladder outlet obstruction from prostate disease, who develop reversible renal failure [48]. These patients have, at some time in their clinical course, high pressure chronic retention of urine and elevated serum levels of ANF, conditions which favor the development of POD. Additionally, the patient's volume status is an important indicator of the degree of diuresis. Hypervolemic patients will diurese more vigorously than those who are euvolemic or volume depleted [35].

Once the obstruction has been treated by catheterization, stenting, or percutaneous nephrostomy, treatment of POD must begin. Hourly assessment of the patient's urine flow and oral intake along with assessment of volume status is essential to prevent the patient from becoming volume depleted. Remembering that the recently unobstructed kidney requires time to recover the ability to conserve sodium and to concentrate urine, the clinician may find it useful to categorize these patients into low, moderate, and high risk of developing diuresis [33] (Figure 5).

In the low-risk and moderate-risk patient, the diuresis may not be brisk, and the thirst mechanism will compel the patient to increase oral intake and replace volume. Obviously if the patient is obtunded, then the thirst mechanism is unreliable, and oral intake will be both inadequate and unsafe. If the patient is nauseated and/or vomiting, oral intake is again unreliable, and if there is orthostatic hypotension, tachycardia, or urine volumes > 200 mL/hour, IV replacement is necessary. The high-risk patient will have evidence for volume overload, mental status changes due to uremia or other neurologic conditions, and almost always complete obstruction of both kidneys or a solitary functioning kidney. These patients should receive IV fluid replacement from the onset of POD.

When IV fluid replacement is needed, a solution with a composition similar to that of urine is desirable. A spot urine for sodium, potassium, and chloride is helpful in determining the makeup of this solution. Urine sodium and chloride are usually 70 – 80 mmol/L. Urine potassium is usually 20 – 30 mmol/L. Therefore, replacement of urine with half normal saline or 5% dextrose in half normal saline with 20 – 30 mmol K/L is ideal in this situation. Since patients requiring immediate IV therapy are often volume overloaded, replacement of each mL of urine with one half mL of IV solution will correct the volume expansion while avoiding volume depletion. If the patient is hyponatremic, then normal saline should be used initially at 1/2 mL IV /mL urine. If the patient is volume depleted on physical assessment, the patient should be given IV normal saline at least 1 IV mL urine and additional boluses of normal saline until euvolemic by physical assessment or by central venous pressure monitoring. If the patient is hyperkalemic at the start of IV replacement, monitoring of the serum potassium will be necessary until the patient is

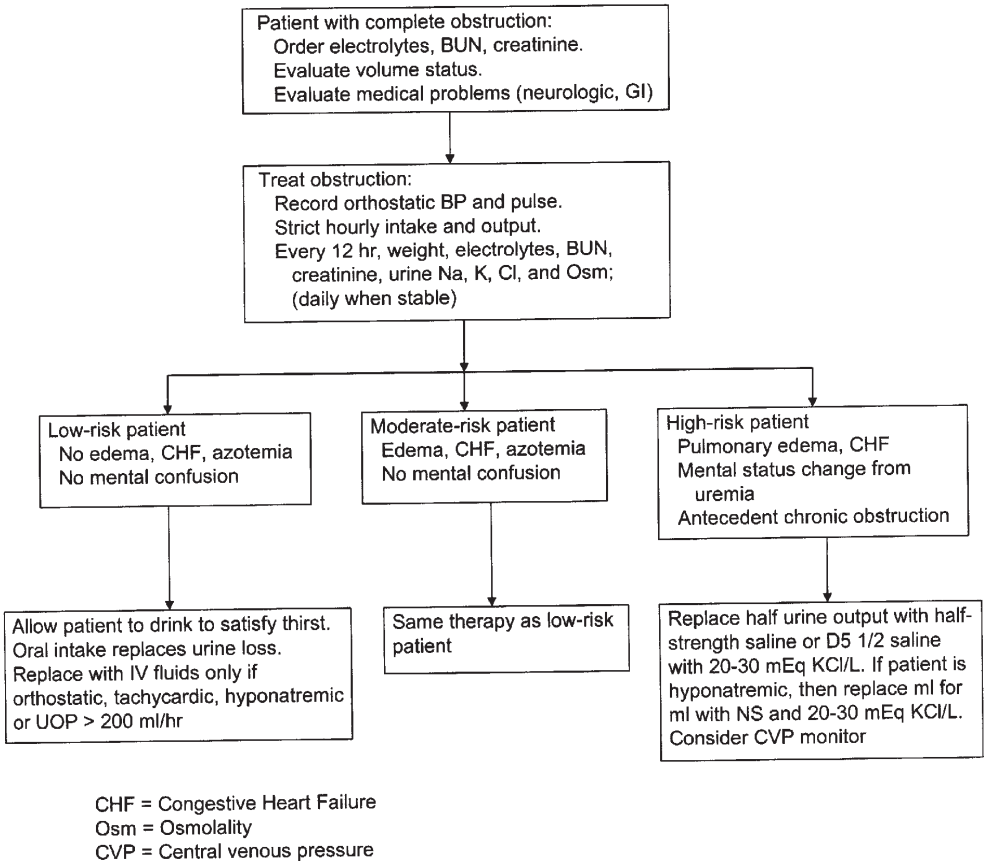

Figure 5. Algorithm for managing postobstructive diuresis. Adapted from [Vaughan ED Jr, Gillenwater JY, Bruce RG, Waid TH, Lucas BA 1997 Understanding postobstructive diuresis. Contemp Urol 9:53-66] with permission. CHF = Congestive Heart Failure, Osm = Osmolality, CVP = Central venous pressure.

normokalemic. Potassium may then be added to the IV urine replacement solution. During the period of recovery of renal function and volume replacement, serum magnesium must be monitored because magnesium wasting can occur in POD. Replacement with magnesium sulfate 0.25 to 0.5 mmol/kg in 4 divided doses daily for the next 24 – 72 hours should be adequate to replace magnesium deficits in these patients [35].

It should be noted that IV fluid replacement is recommended by some authors even in mild cases of POD and in volume overloaded patients [49]. IV fluid administration may result in increased diuresis and natriuresis; however, GFR may recover more quickly. Finally, one must understand that prolonged diuresis can be iatrogenic due to IV volume expansion. When IV fluid replacement is used in patients who are not volume depleted, the clinician should discontinue treatment every 8 – 12 hours. Discontinuation of therapy should produce a slowing of iatrogenic diuresis, whereas POD will continue unabated. One should re-

member that the obstructed kidney has transiently lost its ability to transport chloride and sodium from the lumen of the loop of Henle to the medullary interstitium. The urine concentration of sodium should be high until medullary tonicity is restored, a process requiring urea. If IV fluids are administered too vigorously, the urea concentration will be lowered and the medullary interstitium will be "washed out", delaying the recovery of concentrating ability. In this scenario, the clinician should allow the BUN to rise and follow the urinary sodium. As medullary tonicity rises and the ability to concentrate urine and conserve sodium is restored, the urinary sodium will fall, heralding the slowing of the diuresis within 24 – 48 hours [35].

Summary Points of POD

In summary, it should be remembered that POD stems from the relief of complete urinary obstruction (all functioning nephrons) and is usually, but not always, associated with significantly advanced but reversible renal failure. Urinary concentrating defects begin during the obstructive phase and are not resolved until alleviation of the obstruction and restoration of the hypertonic renal medullary gradient, via the countercurrent exchanger. Natriuresis occurs after the relief of complete obstruction because of defective sodium handling in the proximal and distal tubules. Additionally, the loss of renal medullary function (countercurrent multiplication) presents more sodium and chloride to a relatively nonresorptive distal tubule and collecting duct producing a solute-enriched urine. ANF levels are elevated in volume-expanded states, such as complete urinary tract obstruction, and facilitate a diuresis when the patient is no longer obstructed. An osmotic diuresis from retained urea also occurs.

Although volume overload may be present initially, it can progress to volume depletion when untreated diuresis occurs. In this case, IV fluid administration is needed to prevent prerenal azotemia and possibly shock. However, iatrogenic volume expansion from overzealous administration of IV fluids may prolong the diuretic phase. Advanced but generally reversible renal failure, an acquired distal nonhypokalemic renal tubular acidosis (Type IV RTA) and salt-wasting nephropathy are often present, and other significant electrolyte losses (magnesium, potassium, and chloride) can occur and require replacement. Treatment regimens must be individualized to the patient's volume status, severity of diuresis, mental status, and degree of electrolyte abnormalities. In this regard, vigilant monitoring of the patient's physical status as well as serum and urine chemistries remains the basis of optimum clinical care.

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Nephrolithiasis

Gilberto B. González and Charles Y.C. Pak

Introduction

Kidney stones, formed within the upper urinary tract, are concretions of different mineral salts mixed with an organic matrix. Nephrolithiasis has plagued humans since antiquity. The oldest urinary calculi on record actually comes from an Egyptian mummy dated about 4800 BC. A renal colic due to stone was the first renal disease described by Hippocrates. Considered a classic, this description included a differential diagnosis between renal and bladder stones [1]. Galen (AD 130) was the first to associate stones with a metabolic origin [2]. Some of the notable figures in history who suffered from stones include Pliny, Sir Walter Scott, Benjamin Franklin, Napoleon, and Lyndon B. Johnson [3].

During the past 20 years, notable advances have been made in the nephrolithiasis field. Pathophysiologic mechanisms for many causes of stones have been clarified, and specific molecular defects are beginning to be unraveled [4, 5]. It is now possible to diagnose the cause of stone disease in > 95% of patients [6], and new drugs provide improved treatment options [7 – 9]. Facilitated stone removal has become possible with the introduction of the endoscopic approach [10] and extracorporeal shock wave lithotripsy (ESWL) [11].

Despite these advances, only a few practicing physicians avail themselves of new diagnostic methods and preventive treatment modalities in the management of stone disease. Reasons for this lapse are 2 fold. First, the facility with which stones can now be removed has led to a disparagement of the need for medical diagnosis and treatment. Why bother to have tests done and take drugs for a long duration, when one feels well between stone episodes? Instead, all one has to do is to undergo lithotripsy when, once in a while, a stone is formed and causes trouble.

Second, our group advocated a selective treatment approach that necessitated a careful differentiation of various causes of stones and the selection of specific drugs for each cause. The complexity of this process may have led some physicians to forego the medical approach. However, urinary stone risk factors are not modified by urological procedures alone [12], and nephrolithiasis carries a lifetime recurrence rate as high as 80% [13]. Consequently, a medical approach, directed at prevention of recurrent stone formation, is still required. Strict adherence to the selective approach seems impractical except at a large stone research center. In this chapter, a new and simplified approach for the medical management of kidney stones is proposed, which any physician may readily adopt.

Epidemiology

More than 95% of urinary stones encountered in developed countries are localized in

the kidney or upper urinary tract. Bladder stones are found most commonly in men with prostatic diseases and children who live in less-developed countries in Southern Asia and the Middle East. These stones, related to malnutrition or infection, are a different entity from nephrolithiasis and will not be discussed in this chapter. The true incidence of nephrolithiasis is not well known. Most of the studies have underestimated the problem because they relied on data from hospital records. As many as 70% of patients will not require hospitalization [14]. In an attempt to address this issue, Johnson et al. [15], studied the incidence and prevalence rates for symptomatic, noninfected renal stones over a 25-year period in a well-defined population of Rochester, Minnesota. They found an annual age-adjusted incidence rate for males of 123.6 per 100,000 population in 1974, a 57% increase from 1950. The incidence rate for females was stable over the study period at 36.0 per 100,000. The peak incidence occurs between the ages of 15 – 44 years, during the most productive years [14]. Recurrence rates increase with follow-up: 14%, 35%, 52%, and 75% after 1, 5, 10, and 20 years from the first stone episode, respectively [16, 17]. Thus, recurrence is the rule rather the exception.

Based on this and other population studies, it has been estimated for the United States population that 5 – 15% will have symptomatic stone disease by the age of 70, with the prevalence being twice as common in men as in women. Worldwide, the lifetime stone prevalence in men > 60 years of age varies from 1.5% in China, to 5.4% in Japan, around 8% in the United Kingdom, Germany and Sweden, 12% in Canada, and 20% in Saudi Arabia [18]. Obviously, these differences can be explained in part by variations in study design, but they also reflect real changes due to genetic, nutritional, and environmental influences.

Nephrolithiasis leads to considerable morbidity – renal colic, hematuria, and infection (UTI). It accounts for 0.9% of hospital discharges, with a mean duration of hospital stay of 3 days. The total annual cost in the United States, including direct costs from hospitalization and outpatient evaluation, and indirect costs from lost wages, was estimated to be $1.83 billion in 1993 [19]. In addition, loss of kidney function may occur because of complications such as infection and obstruction, and from damage during surgery. Up to 1% of patients in a dialysis program developed end-stage renal disease (ESRD) secondary to stones [20]. Mortality from stone disease is rare and data are not available.

Stone Composition

Mineral salts, mostly in a crystalline form, account for > 95% of the weight of a kidney stone. A heterogeneous material called matrix is found in concentric layers or radial striations throughout the stone and explains the remaining weight.

The composition of the different crystalline components in stones varies from one part of the world to another, depending on specific methods of analysis and prevalence of stone risk factors. Infrared spectroscopy and X-ray diffraction crystallography offer the highest degree of certainty for the correct analysis of the stone [21]. The most recent series of stone composition based on those techniques for some industrialized countries are summarized in Table 1 [21 – 23]. The majority of stones are mixtures of 2 or more components. Calcareous stones, occurring as calcium oxalate alone or in combination with apatite, comprise approximately 75% of all stones. Cal-

Table 1. Frequency of Occurrence of Components in Renal Stones

Stone type	Mineral name	Mandel 1989 USA (10,163)	Leusmann 1990 Germany (5,035)	Daudon 1995 France (10,438)
I) Calcareous stones				
Calcium oxalate monohydrate	Whewellite	55.4	70.2	42.8
Calcium oxalate dihydrate	Weddellite	34.6	43.6	23.2
Basic calcium phosphate	Apatite	26.9	51.0	15.3
Calcium hydrogen phosphate	Brushite	1.7	2.1	1.0
II) Non-calcareous stones				
Magnesium ammonium phosphate	Struvite	12.6	10.1	2.8
Uric acid		12.6	10.0	8.8
Cystine		0.5	1.0	1.2
Miscellaneous		2.3	2.1	2.4

Numbers indicate the percentage occurrence of the most common stone type in the series. In parentheses is indicated the number of stones.

cium oxalate crystals are found in monohydrate and dihydrate forms, which have different lattice structures and microscopic appearances. Only 5% of stones are principally made of calcium phosphate salts such as apatite or brushite. Noncalcareous stones account for no more than 20% of stones. Struvite stones comprise 5 – 10% of stones; they are often called infection stones because they develop from infection of the urinary tract with urea-splitting organisms. Pure struvite stones are rare; they typically occur as mixtures with carbonate apatite or other calcium salts. Uric acid, the major end product of purine metabolism, accounts for 5 – 10% of stones in Europe and United States. However, endemic regions exist in the Mediterranean countries and in the Near East, where up to one third of all stones are composed of uric acid [24]. Cystine stones, comprising about 1%, are diagnostic of cystinuria, an inherited disorder of dibasic amino acid transport. The miscellaneous group (approximately 2%) includes rare forms of stones such as 2,8-dihydroxyadenine and xanthine (due to inborn errors of metabolism), triamterene or silica (from drug treatments), or matrix calculi (which contain mostly organic molecules and occur in association with chronic UTI) [25, 26].

Stone matrix is composed of about 64% protein, 12% organic ash, 10% bound water, 9% nonamino sugars, and 5% glucosamine. These organic materials might not only derive from substances normally present in urine, but may also be produced by epithelial cells from the trauma induced by an enlarging stone [27].

Pathogenesis

Nephrolithiasis is a heterogeneous disorder; stone composition and the underlying

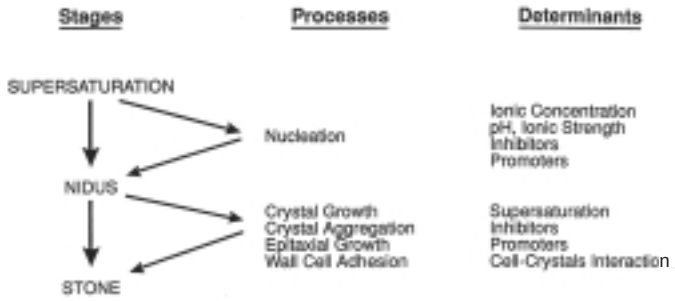

Figure 1. Pathogenesis of stone formation. (Adapted from Pak CYC 1993 Urolithiasis. In: Schrier RW, Gottschalk CW (eds): Diseases of the Kidney (Fifth Ed). Little, Brown and Company, Boston, figure 25-1, p 73, with permission).

mechanisms responsible for stone formation are diverse. Three principal theories of stone formation have been invoked. The precipitation-crystallization theory considers stone formation to be a physicochemical process of precipitation of stone-forming salts from a supersaturated urinary environment [28]. The inhibitor theory holds that a deficiency in urine of substances that physicochemically prevent crystallization leads to stone formation [29]. In the matrix theory, the stone is believed to form in an organic matrix, analogous to the mineralization of the bone [30]. While none of these theories is exclusive of the others, the precipitation-crystallization theory has the most experimental support.

A current scheme for stone formation considers the process to begin by nucleation of a crystal nidus from a supersaturated urinary environment, followed by transformation of the nidus into a stone through crystal growth, epitaxial growth, and crystal aggregation (Figure 1) [31]. This scheme is consistent with all three classic theories, because stones could form without or within an organic matrix and because lack of inhibitors could facilitate the process.

By whatever mechanism, the necessary condition that must occur for stones to form in human urine is nucleation, defined as the beginning of a crystalline solid phase. Homogeneous nucleation refers to the process of spontaneous crystal formation that occurs for any stone-forming salt when its urinary saturation exceeds the limit of metastability. However, in a complex solution such as urine, many foreign surfaces are constantly present cell debris, epithelial membranes, another crystal species (e.g.), and crystals may nucleate on such foreign surfaces in a phenomenon known as heterogeneous nucleation. Because it is not necessary to reach a critical cluster size for nucleation, it is more likely that heterogeneous nucleation occurs at lower levels of metastability [27]. This process may also be the basis for the formation of stones of mixed composition. Examples of heterogeneous nucleation are nucleation of calcium oxalate by seeds of calcium phosphate or by uric acid. The urinary environment of patients with stones is typically supersaturated with respect to stone constituents and possesses a reduced limit of metastability. Thus, the nucleation process is facilitated in the stone-forming urinary environment. This increased propensity for nucleation is reflected, for instance, by the reduced amount of soluble oxalate or calcium required to elicit spontaneous precipitation of calcium oxalate and calcium phosphate in urine of stone-forming patients [32, 33].

Once a crystal nidus has been formed, other events must occur to allow this nidus to become large enough to get lodged in the urinary tract. In principle, the retention of particles within the renal tubule can occur through several mechanisms: by the addition of new

crystals of the same chemical composition to the nucleus (crystal growth); by agglomeration of preformed crystals into large clusters (crystal aggregation); or by epitaxial growth, the process whereby material of one crystal type is precipitated upon the surface of another whose lattice dimensions are almost identical. Alternatively, the stone-forming crystals may react with components of the renal tubular cell, become attached, and grow [27, 34].

Supersaturation of crystalloids can result from the following processes:

- An increase in free ion concentrations, through too little urine output (a concentrated urine), an absolute increase in the amount of a stone-forming constituent excreted in urine (such as calcium, oxalate, uric acid or cystine), or a reduction in natural ligands (such as citrate, which forms a soluble complex with calcium).
- An alteration in the urine pH, because low urinary pH (< 5.5) increases urinary saturation of uric acid, whereas high urinary pH raises that of calcium phosphate and magnesium ammonium phosphate.
- A change in the ionic strength, which alters the ionic activity of stone-forming constituents [34].

Several methods for assessing supersaturation levels in urine have been reported [27, 35]. The urinary activity product provides the best estimate for the state of saturation with respect to stone-forming ions. It is calculated for any given salt, such as calcium oxalate, by estimating ionic activities with a computer program. When the activity product, e.g. $[Ca^{2+}] \times [Ox^{2-}]$, is divided by the corresponding thermodynamic solubility product (solubility product of calcium oxalate in artificial solutions), a relative saturation ratio is derived [35]. A value > 1 represents urinary supersaturation, whereas a value < 1 indicates undersaturation.

Despite the importance of supersaturation in stone formation, the urinary environment of normal subjects without stones is often supersaturated with respect to calcium oxalate, the most common stone salt. To explain lack of stone formation, studies during the past 40 years have sought the presence of inhibitors that retard crystallization processes, particularly of calcium oxalate. These substances have been defined as molecules that raise the metastable limit (so that nucleation would be initiated at a higher supersaturation), inhibit secondary nucleations, or reduce the growth rate and aggregation of crystal nuclei [36]. The mechanism of action appears to be the adsorption of the inhibitors to specific growth sites on the crystal surfaces, which are thought to be dislocations in the crystal lattice. This adsorption prevents the further deposition of crystal lattice ions and prevents the crystals from "sticking" together in an aggregation process [34]. A list of proposed inhibitors is shown in Table 2. Macromolecular inhibitors have been isolated from

Table 2. Urinary Crystallization Inhibitors

I) Low-molecular-weight substances
1. Citrate
2. Magnesium
3. Pyrophosphate
4. Trace metals

II) High-molecular-weight substances
1. Glycosaminoglycans
2. Nephrocalcin
3. Prothrombin F1 peptide
4. Tamm-Horsfall protein
5. Uronic acid rich protein
6. Uropontin

the soluble part of the organic matrix of kidney stones or in the urine. Small molecules (citrate and pyrophosphate) play a prominent role in the inhibition of crystal growth of calcium phosphate [37], whereas larger molecules [36] (glycopeptides and glycosaminoglycans) are believed to play a prominent role in the inhibition of calcium oxalate crystallization. Urinary excretion of some of these inhibitors, e.g. citrate [38] and glycosaminoglycans [39], has been reported to be reduced in some patients with stones. In other studies, Tamm-Horsfall protein and nephrocalcin have been reported to be structurally and functionally abnormal in recurrent calcium oxalate stone formers. However, the role of these organic macromolecules in the pathogenesis of nephrolithiasis has not been well established. Finally, epithelial cell injury and the response of renal cells to crystals might be relevant to the effective growth of renal calculi [40, 41].

Other factors, such as anatomical abnormalities, predispose to stone formation. Nephrolithiasis may be found in association with ectopic, polycystic, or horseshoe kidney, or with stenosis at all levels of the urinary tract. In these conditions, it is generally accepted that secondary urinary stasis predisposes to infection stones or exaggerates stone disease. Medullary sponge kidney is often associated with calcareous renal calculi. There is no convincing evidence that this structural abnormality causes stone formation, because patients with medullary sponge kidney and stones have the same spectrum of biochemical abnormalities as the overall population of stone formers without tubular ectasia [26].

In summary, the pathogenesis of nephrolithiasis is multifactorial and involves alteration in physicochemical and biological mechanisms that regulate the solubility of the urine. Not all aspects of stone formation are well understood, and the exact site in the kidney at which initial steps in stone formation take place is unknown. However, from a clinical point of view, abnormalities or risk factors that predispose to stone formation can be identified in most patients with stones from analysis of their urine.

Urinary Risk Factors for Nephrolithiasis

The frequency and pathogenetic significance of most important urinary risk factors for renal stones are described in Table 3. Data from 1,270 patients with recurrent nephrolithiasis studied during the last 20 years under the same ambulatory protocol were considered in estimating the relative frequency of various risk factors [6]. No abnormality was found in only 4% of patients. Several independent disturbances may, in fact, coexist in a given patient. The co-occurrence of various derangements could be explained by (1) superimposition of a dietary or environmental aberration on an underlying metabolic abnormality, (2) coexistence of separate metabolic abnormalities in the same patient (e.g. distal renal tubular acidosis (RTA) causing hypercalciuria and hypocitraturia), and (3) primary metabolic abnormality causing other derangements (e.g. increased intestinal calcium absorption, leaving less calcium remaining in the gut to bind oxalate, thus resulting in hyperoxaluria).

Hypercalciuria

Hypercalciuria is the most common underlying abnormality, encountered in approxi-

Table 3. Incidence and Pathogenetic Significance of Risk Factors for Nephrolithiasis

Risk factor	Incidence (%)*	Effect in Urine
Hypercalciuria	61	Increased saturation of calcium oxalate and calcium phosphate Reduced inhibitor activity against crystallization of calcium salts by binding negatively charged inhibitors (citrate, chondroitin sulfate) and inactivating them
Hyperuricosuria	36	Increased saturation of monosodium urate Facilitated calcium oxalate crystallization by heterogeneous nucleation or binding macromolecular inhibitor
Hypocitraturia	31	Increased saturation of calcium salts via reduced calcium binding Reduced inhibitor activity against spontaneous nucleation and agglomeration of calcium oxalate,crystal growth of calcium phosphate and heterogeneous nucleation of calcium oxalate by monosodium urate.
Low urine volume	15	Increased saturation of stone-forming salts
Low urinary pH (pH < 5.5)	10	Low uric acid solubility
Hyperoxaluria	8	Increased saturation of calcium oxalate
Hypomagnesiuria	7	Increased saturation of calcium oxalate from reduced binding of oxalate
High urinary pH (pH > 7.0) (struvite stones)	6	Increased saturation of calcium phosphate Increased saturation of struvite (if ammonium ion concentration is high)
Cystinuria	1	Increased saturation of urine

*Represents percentages of patients among 1,270 stone formers studied in Dallas who had each risk factor, either singly or concurrently.

mately 60% of patients with stones. It is usually defined in adults on an unrestricted diet (about 1 g of calcium intake) as urinary calcium excretion in 24 hours > 250 mg in women and 300 mg in men, or 4 mg/kg body weight in patients of either sex [42]. When calcium intake is restricted for one week to 400 mg/day and sodium intake to 100 mEq/day, the upper limit of normal for urinary calcium excretion is 200 mg/day [43].

The association of hypercalciuria with nephrolithiasis was first recognized by Flocks [44]. A pathogenetic role for hypercalciuria in stone formation is supported by several lines of evidence. First, the urinary saturation of calcium oxalate and calcium phosphate has been shown to correlate directly with urinary calcium concentration. Moreover, the urinary environment of patients with hypercalciuric nephrolithiasis was typically supersaturated

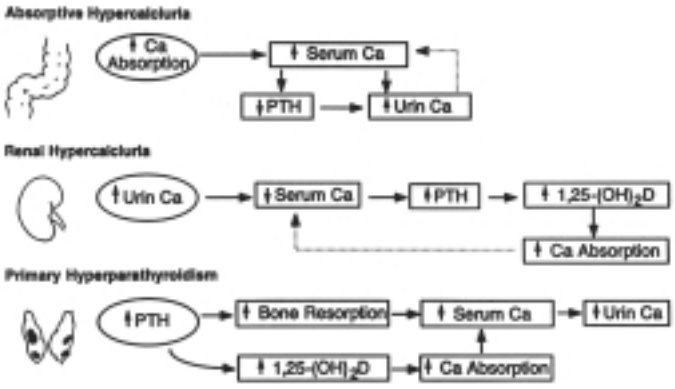

Figure 2. Schemes for the major forms of hypercalciuria. (From Pak CYC 1990 Hypercalciuric calcium nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 3-5, p 44, with permission.)

with respect to these salts [33]. It was initially suggested that hyperoxaluria was more effective than hypercalciuria in augmenting the urinary saturation of stone-forming calcium salts [45]. However, a reexamination of the problem disclosed an equivalent action of calcium and oxalate. Within the range of concentrations encountered in urine, the rise in calcium concentration was as effective as the increase in oxalate concentration in raising the urinary saturation of calcium oxalate [43]. Indeed, correction of hypercalciuria with the administration of thiazides [46] or sodium cellulose phosphate [47] has effectively reduced stone formation in hypercalciuric patients. Second, hypercalciuria may reduce the inhibitor activity in urine by binding negatively-charged inhibitors and inactivating them. Thus, Zerwekh and colleagues reported that the inhibition of spontaneous nucleation of calcium oxalate exhibited by citrate and chondroitin sulfate was reduced by calcium [48]. Lastly, failure of medical therapy in some patients with calcium nephrolithiasis has been associated with persistent hypercalciuria [49].

Most patients with hypercalciuric nephrolithiasis are normocalcemic and have no obvious cause for increased calcium excretion. The term idiopathic hypercalciuria was used by Albright et al. to denote this entity [50]. Pak, et al. broadly categorized hypercalciuria of nephrolithiasis into 3 types (Figure 2) [43].

Absorptive hypercalciuria (AH), the most common stone-forming entity [6], is characterized by a primary enhancement of intestinal calcium absorption. Following oral calcium ingestion, there is a transient hypercalcemic response which leads to hypercalciuria by enhancement of renal filtered load of calcium and suppressed secretion of parathyroid hormone (PTH), a hormone known to increase renal reabsorption of calcium. AH appears to be inherited as an autosomal dominant trait [51]. Our group in Dallas have devoted considerable effort to delineating the pathophysiology of this disturbance. Although increased circulating calcitriol concentrations have been reported for AH patients and could explain the elevated intestinal calcium absorption, we have not observed frank elevations in serum calcitriol in the majority of our patients [52]. This observation suggests that vitamin D-independent processes or increased intestinal sensitivity to the action of vitamin D might be operative in a majority of the AH patients.

When patients with AH are challenged with a short course of ketoconazole, an inhibitor of steroid synthesis, the ensuing reduction in

calcitriol synthesis produces a decline in intestinal calcium absorption and in urinary calcium in some, but not all, patients [53]. This finding suggests some dependency or sensitivity of the gut to the prevailing concentration of 1,25-$(OH)_2D_3$. Furthermore, we previously reported increased vitamin D receptor (VDR) numbers in activated lymphocytes from some patients with AH who had normal circulating 1,25-$(OH)_2D_3$ levels [54]. These observations, as well as a report of increased intestinal VDR concentration in the genetic hypercalciuric rat [55], an animal model with a phenotype similar to that of the human disease, all prompted a detailed examination of VDR expression in patients with AH. However, extensive molecular biological studies have so far failed to support a pathophysiological importance of vitamin D. Thus, no alteration was found in the VDR cDNA coding region from patients with AH [56]. The gene for VDR or 1-α-hydroxylase of vitamin D was not linked to the inheritance pattern of AH from linkage analysis [57]. Again, there was neither an increase in VDR levels in skin fibroblasts, a recognized vitamin D-responsive cell, nor increased sensitivity to upregulation of VDR numbers by 1,25-$(OH)_2D_3$ in patients with AH [58]. These studies do not preclude a role of VDR concentration in intestinal tissue from patients with AH, where prolongation of the protein's half-life may promote increases in intestinal calcium absorption, hypercalciuria, and nephrolithiasis. Moreover, there may be involvement of other vitamin D responsiveness genes.

Renal hypercalciuria and primary hyperparathyroidism each account for no more than 2% of patients with renal stone disease [6]. In renal hypercalciuria, there is a primary renal leak of calcium, with a transient hypocalcemia. This stimulates parathyroid function, and the excess of PTH leads to calcium mobilization from bone and increased intestinal calcium absorption via 1,25-$(OH)_2D_3$. The cause for the renal leak of calcium is not known. The restoration of normal serum PTH, 1,25-$(OH)_2D_3$ and intestinal calcium absorption upon correction of renal calcium leak by thiazide supports the proposed pathogenetic scheme [59]. Resorptive hypercalciuria is most commonly due to primary hyperparathyroidism. The excessive secretion of PTH stimulates bone resorption, increasing serum calcium and renal filtered load of calcium. Furthermore, PTH-induced renal synthesis of 1,25-$(OH)_2D_3$ leads to enhanced intestinal calcium absorption, leading to further increase in serum calcium and filtered renal calcium load.

Some hypercalciuric patients cannot be categorized into these major variants. Many of them present with fasting hypercalciuria with normal parathyroid function. This presentation may reflect abnormal renal clearance of absorbed calcium in patients with absorptive hypercalciuria. However, recent studies suggest that in some of these cases, hypercalciuria may be partly skeletal in origin because of cytokine-induced bone resorption [60].

Hyperuricosuria

The association of hyperuricosuria with uric acid stone formation is universally recognized [61]. However, it is less commonly realized that hyperuricosuria is also associated with the formation of calcium oxalate stones, even in the absence of hypercalciuria or hyperoxaluria. This association was first noted by Coe et al. who reported that these patients respond favorably to treatment with allopurinol [62].

Figure 3 explains calcium stone formation in the setting of hyperuricosuria, although this scheme has not been clearly validated [63] (Figure 3). Hyperuricosuria, in the setting of

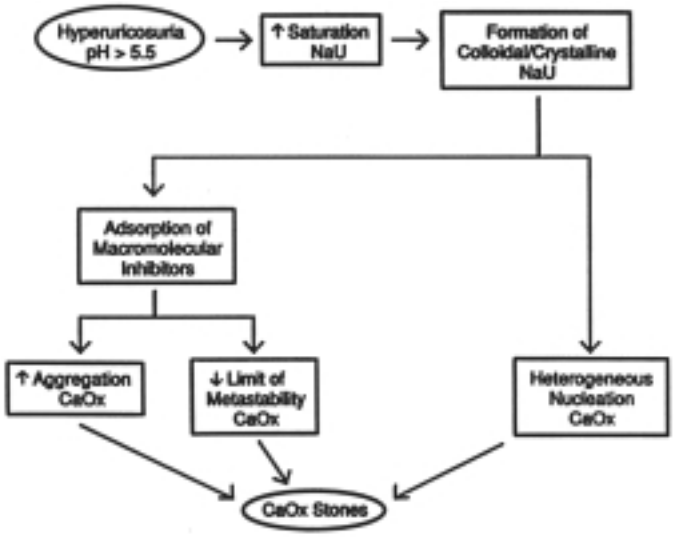

Figure 3. Scheme for calcium oxalate stone formation from hyperuricosuria. NaU = monosodium urate; CaOx = calcium oxalate. (From Pak CYC 1990 Hyperuricosuric calcium nephrolithiasis . In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 5-1, p. 80, with permission.)

normal pH at which adequate dissociation of uric acid occurs, produces urinary supersaturation of monosodium urate. The resulting formation of colloidal or crystalline monosodium urate causes formation of calcium oxalate stones by heterogeneous nucleation [64, 65], or by adsorption of macromolecular inhibitors [66].

The usual upper limits for normal uric acid excretion are 750 mg/day in women and 800 mg/day in men. However, urine specimens with normal pH of 6.4 were invariably supersaturated when the content of the total dissolved urate exceeded 300 mg/L [63]. Thus, a more functional definition of 600 mg/day for normal upper limit of uric acid excretion is employed in our laboratory at Dallas, assuming a desired urine volume of 2 L/day. Depending on the definition used for hyperuricosuria, it is present in 20 – 40% of the stone-forming population.

The most frequent cause for hyperuricosuria is a purine-rich diet (red meat, poultry and fish). Recurrent stone formation can be ameliorated by dietary purine deprivation [63]. In a minority of patients, hyperuricosuria results from urate overproduction (e.g. myeloproliferative disorders) or uricosuric drugs (e.g. high doses of aspirin).

Hypocitraturia

Citric acid is a tricarboxylic acid with pKa's of 2.9, 4.3, and 5.6. Therefore, in plasma, citrate exists predominantly as a trivalent anion, citrate^{-}. Intracellular citrate is a key component of the tricarboxylic acid cycle (Krebs' cycle), in which ATP is produced from glucose and other fuels [67]. Citrate represents the most abundant of the organic anions and acids present in the urine and plays an important role as an inhibitor of the crystallization of calcium salts.

The physicochemical action of citrate is summarized in Figure 4. Citrate probably acts chiefly through the formation of a complex with calcium, causing a reduction in the ionic calcium concentration and the urinary saturation of calcium oxalate and calcium phos-

Figure 4. Scheme for the inhibitor activity of citrate. (From Pak CYC 1990 Hypocitraturic calcium nephrolithiasis In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 6-1, p.91, with permission.)

Table 4. Causes of Hypocitraturia

I) Acidosis
1. Distal renal tubular acidosis
   Complete
   Incomplete
2. Chronic diarrheal syndrome
3. Hypokalemia
4. Strenuous physical exercise
5. High sodium or meat intake

II) Urinary tract infection

III) Idiopathic

phate [68]. In addition, citrate directly inhibits agglomeration of calcium oxalate [69] and spontaneous nucleation of calcium oxalate [70], and may also impair urate-induced crystallization of calcium oxalate [71]. The loss of inhibitor activity of citrate leads to increased saturation, enhanced heterogeneous nucleation, and facilitated crystal growth and aggregation of calcium oxalate (Table 3).

The principal cause for hypocitraturia in nephrolithiasis is acidosis or acid retention (Table 4). Acidosis reduces urinary citrate both by enhancing renal tubular reabsorption and by impairing peritubular uptake and synthesis of citrate. Renal citrate lyase activity is increased by chronic acidosis, leading to reduced intracellular citrate and enhanced tubular reabsorption [67].

Distal acidification defect (type I) is the only form of renal tubular acidosis (RTA) associated with nephrolithiasis. Acidosis is characteristic of distal RTA (due to an inability to excrete acid) and is characterized by systemic metabolic acidosis or defective urinary acidification following an ammonium chloride load, and urinary pH > 6.5 in the absence of UTI. The acidosis is a hypokalemic, hyperchloremic, nonanion gap metabolic acidosis. In the complete form, metabolic acidosis is present before an ammonium chloride load is given. In the incomplete form, urinary acidification following ammonium chloride load is impaired, despite normal serum electrolytes before the load. Chronic diarrheal states are associated with acidosis secondary to intestinal alkali and potassium loss. The degrees of hypocitraturia are generally proportional to the severity of intestinal fluid loss. Hypokalemia, itself a result of intracellular acidosis, may in turn cause hypocitraturia (e.g. during thiazide treatment).

Other causes of acidosis-induced hypocitraturia are strenuous physical exercise (from lactate accumulation), high sodium intake (from bicarbonaturia), and a high meat diet (from increased acid ash content). Hypocitraturia is also found in UTI, probably from the degradation of citrate in urine by bacterial enzymes and bacterial consumption of citrate. In a significant number of cases, there is no apparent cause of hypocitraturia; dietary acid excess may be responsible. Our own studies do not support existence of primary citrate malabsorption. Citrate absorption from the gastrointestinal tract was directly measured by using the intestinal washout technique. In both normal subjects and in patients with stones, citrate absorption was very efficient, with nearly 100% absorption in 3 hours [72 – 74].

Hypocitraturia has been variously reported in 19 – 63% of patients with nephrolithiasis [75]. This variation reflects different normal ranges for urinary citrate established by various laboratories. In the laboratory at Dallas, hypocitraturia is defined by citrate < 320 mg/day for adult men and women [76]. This value of 320 mg/day was derived from a large number of normal subjects in this laboratory. Among stone-forming patients, no significant difference in urinary citrate was found between men and women. In distal RTA, urinary citrate is invariably < 320 mg/day [77]. Finally, this limit provides a good empirical definition of hypocitraturia, because patients with urinary citrate below this level often show a clinical response to potassium citrate therapy that is superior to the response in patients with citrate > 320 mg/day [78]. Using this definition, hypocitraturia was found in 31% of our population of stone-forming patients [6].

Low Urine Volume

Low urine output represents one of the major risk factors, predisposing to all forms of stone disease. It may be the result of an inadequate fluid intake or elevated extrarenal loss of fluid (e.g. chronic diarrhea or excessive sweating in hot climates) [79 – 81]. Failure to increase urine volume has been identified as a predictor of relapse of calcium nephrolithiasis during treatment [49]. Low urine output increased the urinary saturation of all stone-forming salts by increasing the concentration of constituents of the stone. Conversely, urinary dilution was found to reduce the propensity for the crystallization of calcium salts in urine by lowering the urinary saturation of brushite and calcium oxalate, and by increasing the minimum supersaturation needed to elicit spontaneous nucleation of calcium oxalate [80]. With a stringent definition of 1 L/day as the low normal limit of urine volume, 15% of patients had this risk factor [6]. Had we used a higher figure of 2 L/day, indicative of desired urine volume [80], a much higher percentage of patients would have had low urine volume.

Low Urinary pH

The principal determinant of uric acid crystallization is its relative insolubility in the acidic urinary environment. Thus, the solubility of uric acid is pH dependent (Figure 5). Below a pH of 5.5 (the pKa of uric acid), most of the uric acid remains in an undissociated form, possessing a low aqueous solubility of < 100 mg/L [63]. This unusually acid environment leads to the development of uric acid stones. Once a uric acid stone is formed, it could induce formation of calcium oxalate stones by the same mechanisms already mentioned for monosodium urate (see *Hyperuri-*

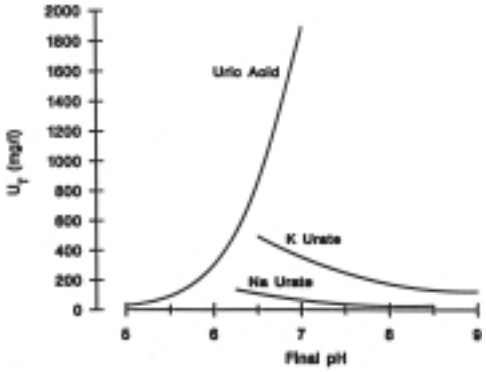

Figure 5. Uric acid solubility and transformation to urate salts. (From Pak CYC 1990 Uric acid nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 7-1, p 106, with permission.)

cosuria). Secondly, the urinary saturation of uric acid increases proportionately with the rise in total uric acid concentration. With a rise in pH, more uric acid becomes dissociated into an anionic form, approaching 100% at pH 6.5. Thus, the propensity for uric acid crystallization is low at higher urinary pH [63].

Low urinary pH could result from environmental or nutritional aberrations, such as dehydration, strenuous physical exercise, and consumption of a diet rich in animal proteins [82]. Undue urinary acidity may be due to metabolic disturbances as well, such as chronic diarrhea [83] or, most often, gouty diathesis [84, 85].

The term gouty diathesis represents the formation of uric acid and/or calcium stones in patients with primary or latent gout. Stones may precede articular manifestations of primary gout in up to 40% of those patients. The 2 types of gouty diathesis, presenting with uric acid stones or calcium stones, share similar clinical and biochemical features characteristic of primary gout. Thus, a substantial percent of gouty diathesis patients have gouty arthritis, hyperuricemia, hypertriglyceridemia, and high renal tubular reabsorption of urate, in addition to a low urinary pH (< 5.5) unaccounted for by dietary acid excess or intestinal alkali loss [84]. The underlying mechanism in gouty diathesis responsible for undue urinary acidity is still unknown. Some patients have decreased ammonium excretion even with normal glomerular filtration rate (GFR), however, the cause for this defective urinary ammonium excretion is unclear [86]. Since there is a reciprocal increase in urinary titratable acidity, no systemic acidosis occurs [87, 88]. Gouty diathesis was found in 10% of recurrent stone-formers [6].

Hyperoxaluria

Oxalate is a useless end product of metabolism and is excreted primarily in the urine. It is clinically relevant to renal stone formation because of the low solubility of its calcium salt (calcium oxalate) [89]. Both in patients with recurrent calcium nephrolithiasis and in normal subjects, urinary saturation of calcium oxalate is directly correlated with urinary oxalate concentration. As mentioned previously, a rise in oxalate concentration is equally effective as a rise in calcium concentration in augmenting the saturation of calcium oxalate [68].

Normally, about 10% of urinary oxalate is derived from diet, 25 – 30% comes from direct metabolic conversion of ascorbic acid and tryptophan, and 60% is attributable to oxidation of glyoxalate. Two major pathways for glyoxalate degradation are its transamination to alanine and glycine. This last step requires pyridoxine (vitamin B_6) as a cofactor (Figure 6) [90].

Hyperoxaluria, defined as a daily urinary oxalate excretion > 44 mg, is found in around 10% of recurrent stone formers [6]. It results from 2 main mechanisms: either intestinal

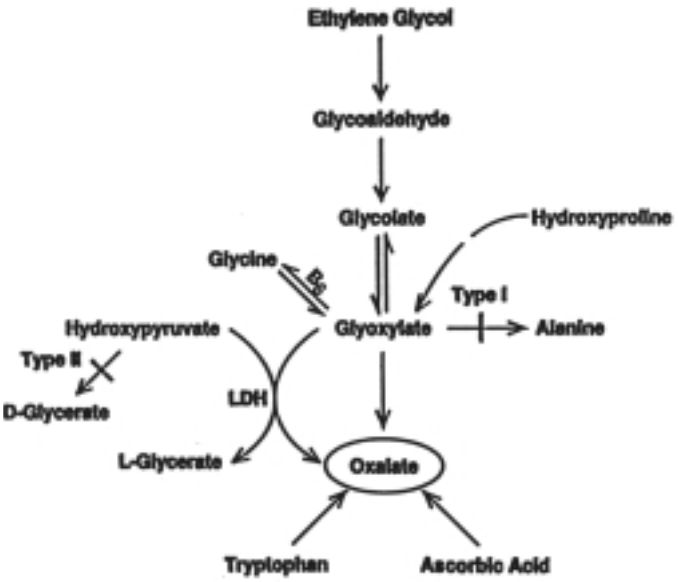

Figure 6. Biosynthetic pathway for oxalate. (From Pak CYC 1990 Hyperoxaluric calcium nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis.: WB Saunders, Philadelphia, figure 4-2, p 68, with permission.)

Table 5. Causes of Hyperoxaluria

I) *Increased intestinal oxalate absorption*
1. High-oxalate diet
2. Enteric hyperoxaluria
3. Low intraluminal calcium concentration

II) *Increased oxalate synthesis*
A) Enzymatic disturbances
1. Primary hyperoxaluria, type 1 and type 2
2. Pyridoxine deficiency

B) Increased availability of precursors
1. Ascorbic acid
2. Ethylene glycol and methoxyflurane

hyperabsorption of oxalate or, less frequently, from increased synthesis of oxalate (Table 5).

In general, only 2 – 5% of oxalate from food is normally absorbed. Foods of high oxalate content are leafy green vegetables, nuts and peanut butter, brewed tea, and chocolate. Slight to moderate hyperoxaluria could develop from an excessive intake of oxalate-rich foods. In such cases, urinary oxalate is normal after one week on a diet poor in oxalate [6, 89]. Enteric hyperoxaluria is defined as hyperoxaluria occurring in patients with ileal disease (Crohn's disease, ulcerative colitis, jejunoileal bypass or intestinal resection) or fat malabsorption (pancreatic insufficiency, celiac sprue or bacterial overgrowth) [83, 90]. Two mechanisms have been implicated. First, the intestinal mucosa may become more permeable to oxalate from the direct action of nonabsorbed bile salts and fatty acids. Second, the nonabsorbed bile salts and fatty acids may complex divalent cations, reducing the amount of free calcium and magnesium in the intestinal lumen. Fewer divalent cations would be available to bind oxalate, leaving an enlarged pool of absorbable oxalate. An intact colon is essential for the development of hyperoxaluria, because it is the principal site of oxalate absorption. The occasional mild hyperoxaluria found in patients with absorptive

hypercalciuria or low calcium intake may occur in a similar fashion from the reduced complexation of oxalate by calcium.

Hyperoxaluria due to increased oxalate synthesis occurs less frequently. Primary hyperoxaluria is an inherited abnormality of oxalate metabolism. Patients with this condition excrete more than 80 mg/day of urinary oxalate. Two types have been well characterized (Figure 5). In type 1, the more common, there is a deficiency of the enzyme alanine:glyoxylate aminotransferase, whereas in type 2 the enzyme D-glyceric dehydrogenase is deficient. The typical sequelae of primary hyperoxaluria are early nephrolithiasis, nephrocalcinosis, systemic oxalosis, and renal failure leading to death [91]. Preliminary data suggest that pyridoxine deficiency may induce hyperoxaluria in some patients; thus, pyridoxine supplementation might be useful in some cases.

Vitamin C in doses > 500 – 1000 mg/day may induce a rise in urinary oxalate by serving as a substrate for oxalate synthesis. A similar mechanism is seen in those rare cases of severe hyperoxaluria (often associated with renal failure) induced by ethylene glycol or methoxyflurane [89].

Hypomagnesiuria

Magnesium inhibits stone formation by binding oxalate, thus reducing the saturation of calcium oxalate. Moreover, it has a modest inhibitory effect on the crystal growth of calcium oxalate [92, 93]. Thus, calcium oxalate crystallization could be enhanced in the setting of hypomagnesiuria. Hypomagnesiuria occurs in chronic diarrheal syndrome from malabsorption of magnesium, thus increasing the risk for nephrolithiasis in patients with bowel disease [94]. In the absence of intestinal disease, hypomagnesiuria, defined as urinary magnesium excretion < 50 mg/day, was present in 7% of patients with stones in the series at Dallas [6]. This entity (termed hypomagnesiuric calcium nephrolithiasis) is probably dietary in origin. Most patients give a history of avoidance of magnesium-rich food [95], and magnesium metabolism has been reported to be normal in patients with calcium nephrolithiasis [96]. Most of the hypomagnesiuric patients also have hypocitraturia.

High Urinary pH

– *Calcium phosphate stones*. Urinary pH has a pronounced effect on the supersaturation of calcium phosphate salts by influencing the dissociation of phosphate to form HPO_4^{2-} (a component of brushite stones) and PO_4^{3-} (a component of apatite) [97]. Thus, at pH < 6.9, brushite ($CaHPO_4 \cdot 2H_2O$) is the predominant phase of calcium phosphate salts, whereas a higher pH favors the formation of apatite ($Ca_5(PO_4)_3(OH)$) [98]. This relationship explains at least some of the mechanisms for the occurrence of calcium phosphate stones in patients with distal RTA [99, 100] or infection.

– *Infection stones*. These stones occur in urine infected with urea-splitting organisms and are composed of a combination of struvite ($MgNH_4PO4 \cdot 6H_2O$) and carbonate-apatite ($Ca_{10}(PO_4)_6CO_3$). Figure 7 illustrates the pathogenesis of infection stones. The action of urease within the urinary tract produces high levels of ammonium, carbonate, and urinary pH > 7.2. The resulting alkalinity of urine increases the amount of trivalent phosphate, as already mentioned. Thus, the urinary environment becomes supersaturated with struvite and carbonate apatite, leading to the crystallization of

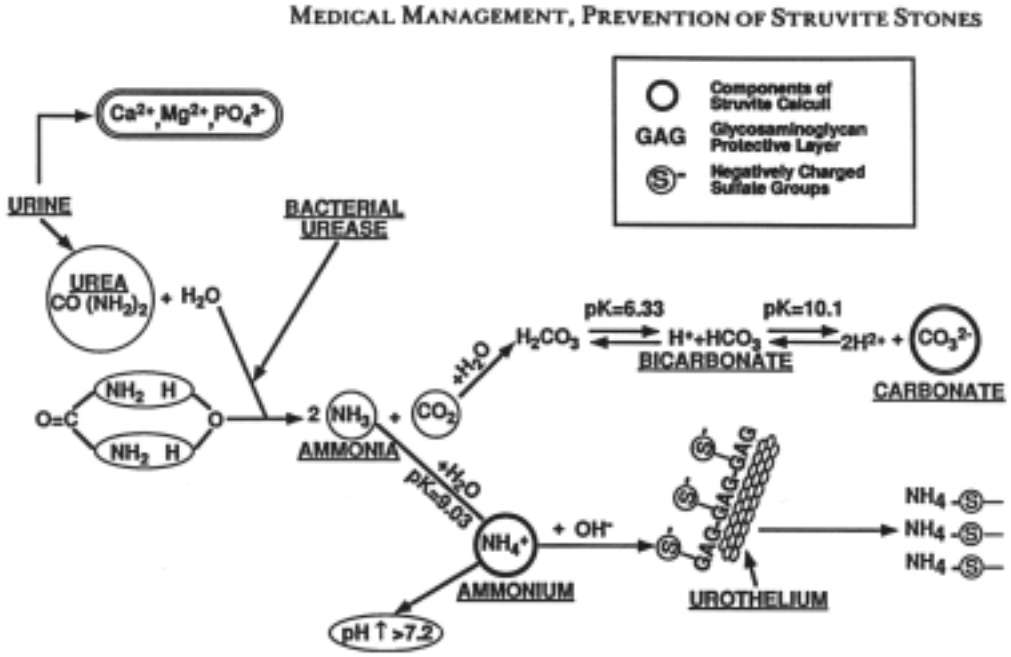

Figure 7. Pathogenesis of stone infection. (From Wong HY, Riedl CR, Griffith DP 1996 Medical management and prevention of struvite stones. (In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GL (eds.): Kidney Stones: Medical and Surgical Management, Lippincott-Raven Publishers, Philadelphia, figure 1, p 943, with permission).

these stone constituents. Moreover, propagation of struvite crystals is enhanced by its adhesion to the sulfate groups of the glycosaminoglycan layer protecting the urothelium. Both factors combined can lead to rapid development of large stones [101]. The experimental evidence suggests that infection stones can be formed only in the presence of urea and urea-splitting organisms. Thus, a high urinary pH alone in the absence of other factors would promote the crystallization of calcium phosphate, but not struvite [102]. Infection stones account for 6% in the series at Dallas [6]. *Proteus* species are responsible for the majority of infection that cause these stones in all age ranges. Other common organisms that produce urease are *Haemophilus influenzae, Staphylococcus aureus, Yersinia enterocolitica,* and *Ureaplasma urealyticum* (this last requires special culture techniques for its detection). *Escherichia coli* does not produce urease and therefore is not responsible for the formation of infection stones [103].

Cystinuria

Cystinuria is an autosomal recessive disease characterized by increased urinary excretion of the dibasic amino acids cystine, arginine, lysine, and ornithine. Only cystine is insoluble enough to precipitate in physiological settings. Thus, the most important pheno-

Table 6. Role of Urinary Risk Factors in the Different Types of Renal Stones

Urinary risk factor	Calcium Oxalate	Calcium Phosphate	Uric Acid	Infection Stones	Cystine
Hypercalciuria	√	√			
Hyperuricosuria	√		√		
Hypocitraturia	√	√			
Low urine volume	√	√	√	√	√
Low urinary pH			√		
Hyperoxaluria	√				
Hypomagnesiuria	√				
High urinary pH		√		√	
Cystinuria					√

√ = risk factor

typic expression of cystinuria is the predisposition toward cystine stones (1% of renal stones) [104].

The main determinant of cystine crystallization is urinary supersaturation. It has also been recognized that the solubility of cystine is pH dependent, with the lowest solubility at the low range of urinary pH, gradually increasing with a rise in pH to 7.5, and rapidly increasing above a pH of 7.5 [105]. There is no inhibitor of cystine crystallization. In the homozygous state (cystine excretion greater than 250 mg/g creatinine in a 24-hour urine collection), cystine stones invariably develop because the solubility limit for cystine is often exceeded [104].

The solute carrier family 3, member 1 (SLC3A1) gene, located on chromosome 2, codes for a protein involved in renal cystine transport. In a recent review, 9 polymorphisms and 21 different mutations were reported in the SLC3A1 gene. Most of them were base substitutions, while others were deletions. Some mutations have been found in a single individual patient, while others have been found in more than individual. Transfection studies indicate that these mutations are responsible for cystinuria. However, some cases of cystinuria are not related to defects in SLC3A1; thus, other genes might also be involved [4].

Table 6 summarizes the role of urinary risk factors in the different types of renal stones.

Medical Management

The primary objective of medical management is the prevention of recurrent stone formation. The medical approach may be fully justified because of the high rate of recurrence characterizing most forms of stone disease. Moreover, medical evaluation may disclose underlying diseases with extrarenal manifestations, such as bone disease in primary hyperparathyroidism or intestinal malabsorption syndrome in enteric hyperoxaluria.

In the past, a selective treatment approach was advocated by Pak and colleagues [51].

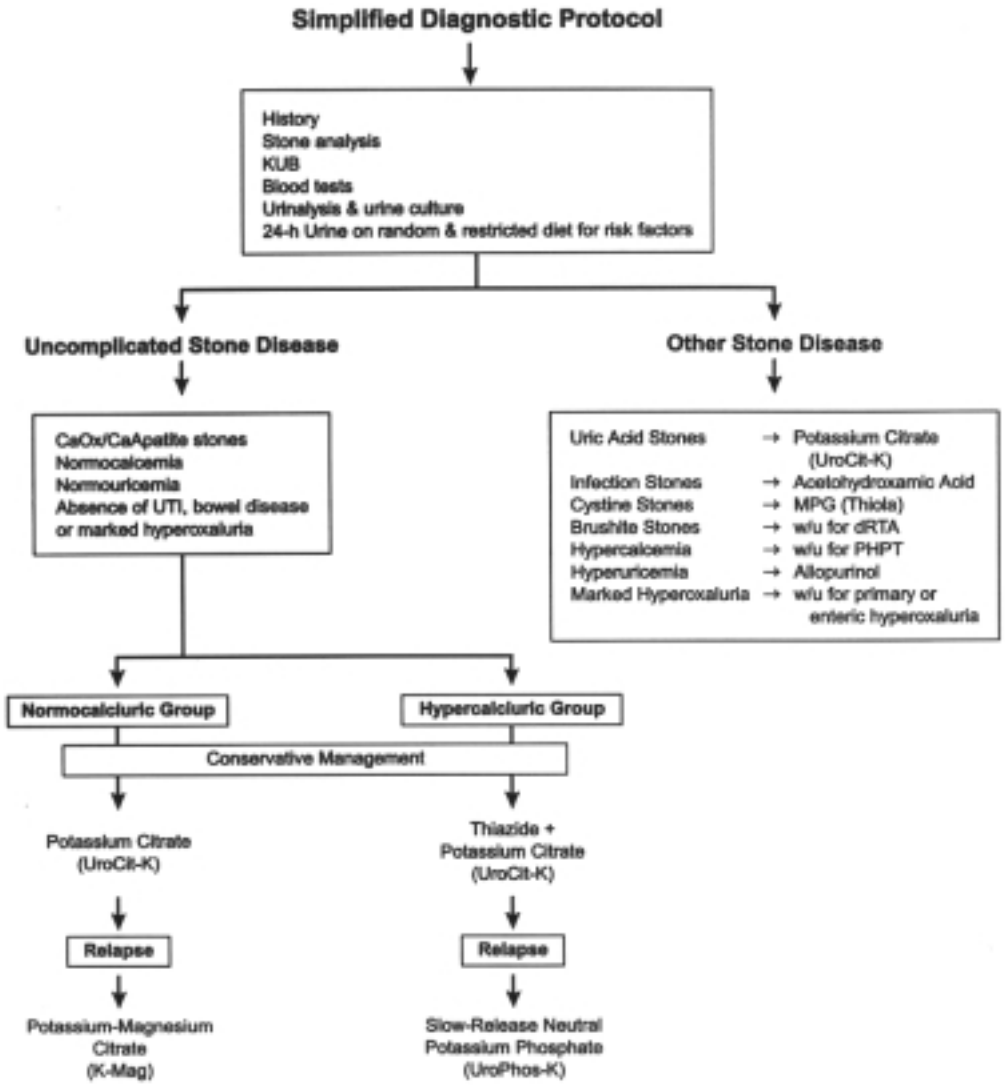

Figure 8. Algorithm for simplified approach to the medical management of nephrolithiasis.

This approach recognized heterogeneity in the pathophysiology of stone disease. After a detailed diagnostic protocol, a specific drug was selected for each cause, based on its ability to correct underlying metabolic derangements. Unfortunately, this approach seems to be too cumbersome for ready adoption for some practicing physicians. In a recent survey of 10 stone research centers from different parts of world, medical drug treatment was used sparingly and nonselectively [106]. Thus, a simplified program for the management of stones which any physician anywhere may readily adopt is described here, in lieu of a selective approach which could be used in large stone research centers.

Table 7. Stone-provoking Medications

Medications	Stone Type	Mechanism
Acetazolamide	CaP, CaOx	Hypercalciuria, Hypocitraturia, High urinary pH
Allopurinol	Xanthine	Enhanced excretion of xanthine
Ca supplements	CaOx, CaP	Hypercalciuria
Ca channel blockers	CaOx, CaP	Hypercalciuria
Loop diuretics	CaOx, CaP	Hypercalciuria
P-binding antacids	CaOx	Hypercalciuria
Silica (Antacids)	Silica	Urinary excretion of silica
Theophylline	CaOx, CaP	Hypercalciuria
Triamterene	Triamterene	Urinary excretion of triamterene
Uricosuric agents	CaOx, UA	Hyperuricosuria
Vitamin C	CaOx	Hyperoxaluria
Vitamin D	CaOx	Hypercalciuria

CaOx: calcium oxalate; CaP: calcium phosphate; UA: Uric Acid

A summary of the simplified program for medical management of nephrolithiasis is shown in Figure 8. This approach was designed to achieve 3 important purposes in medical management of nephrolithiasis.

Separation of Uncomplicated Stone Disease from Other Stone Disease

History

A careful history should be taken during the evaluation of the stone-forming patient, because it may provide clues about the severity, underlying causes and extrarenal manifestations of stone disease. It should focus on: (1) chronology of stone events, such as age of first stone passage and dates of further episodes, number and type of stones passed, spontaneous passage vs. need for surgical intervention; (2) family history of stones or personal history for bone or gastrointestinal disease, gout, chronic urinary tract infection (UTI), or nephrocalcinosis; (3) stone-provoking medications; and (4) nutritional habits [107, 108].

Patients with early onset of nephrolithiasis may suffer from inherited metabolic disorders (e. g. primary hyperoxalurias, xanthinuria, cystinuria) or have a higher risk for calcium stone recurrence. Patients with multiple stones or a family history of stones are also at increased risk of recurrence. A list of the most common medications that could cause or exacerbate stone disease is shown in Table 7. A careful history should also be taken for past medical treatments of stone disease. Their failure may indicate inaccuracy of the original diagnosis or a need for more specific therapy. Nutritional history should be taken, directing particular attention to dietary aberrations implicated in stone formation, such as low fluid intake, high calcium intake, high oxalate diet, sodium excess, animal protein excess, and low citrus fruit intake. The pathogenetic role of some of these factors will be briefly reviewed.

A recent epidemiological study disclosed that, among healthy subjects without stones, high calcium intake may reduce the risk of stone formation [109], attributed to the binding of oxalate by calcium in the intestinal tract. Unfortunately, the concurrent higher intake of potassium (citrus fruits), magnesium, phosphate, and fluids by the high calcium intake group could have clouded interpretation of the results. Moreover, these results may not be extrapolated to stone formers or hypercalciurics, since these two groups were not studied. Physiologically, high calcium intake or calcium supplementation may not confer an increased risk of stone formation in healthy subjects because of the operation of the intestinal adaptation process [110]. During high calcium intake, the fraction of calcium absorbed is decreased because of parathyroid suppression and reduced calcitriol synthesis. In healthy subjects, urinary calcium rose substantially after one month of calcium supplementation, but it decreased toward the pretreatment range during continued treatment for 2 more months [111]. In patients with absorptive hypercalciuria, the intestinal adaptation process may not operate because of the primary enhancement of intestinal calcium absorption [43]. Thus, a high calcium intake provoked a marked increase in urinary calcium that was considerably above the normal range and was apparently sustained. In contrast to healthy subjects, patients with absorptive hypercalciuria may be at increased risk of stone formation from high calcium intake.

The metabolic effect of sodium load has been examined by providing 250 mEq of sodium daily over a basal metabolic diet. As reported previously, urinary calcium increased significantly. In addition, urinary pH increased modestly and urinary citrate decreased significantly. These effects have been ascribed to bicarbonaturia from sodium-induced volume expansion. Commensurate with these changes, sodium load increased the propensity for the crystallization of stone-forming calcium salts [112].

Animal proteins are rich in sulfur-containing amino acids. When they are metabolized, sulfate is released. Thus, a high consumption of animal protein represents an acid load, which could reduce urinary citrate and pH. In addition, urinary calcium may increase because of higher bone resorption and renal calcium leak induced by the transient metabolic acidosis. Uric acid also will increase with an ingestion of all meat products (beef, poultry and fish) since they are rich in purines [113, 114].

Citrus fruits are rich in citric acid and potassium, particularly the former. Their intake is associated with a rise in urinary pH and citrate and occasionally by a fall in urinary calcium. Citrus fruits contain a modest amount of calcium (100 mg/L), vitamin C (< 500 mg/L) and oxalate (0 – 21 mg/L). The amount of these nutrients in fruit juices is probably insufficient to affect stone disease adversely. Thus, the net effect of citrus fruits is beneficial. Conversely, a low intake of citrus fruits may contribute to hypocitraturia, and may enhance the risk for stone formation [108, 115].

The role of a low fluid intake and high oxalate diet was already discussed in the section on urinary risk factors.

Stone Analysis

The diagnosis of different causes of nephrolithiasis is no longer made solely on the basis of stone composition. There is increasing reliance on underlying physiological derangements. However, stone analysis is still important and should be obtained in every stone-forming patient if a sample is available.

The disclosure of cystine, or struvite or carbonate apatite, is diagnostic of cystinuria or infection with urea-splitting organisms, respectively. The presence of 2,8-dihydroxyadenine, triamterene, silica, or xanthine indicates 2,8-dihydroxyadeninuria, treatment with triamterene or magnesium trisilicate, or xanthinuria. In these conditions, the crystallographic identification is critical for the diagnosis; laboratory and clinical data provide supporting evidence. For the remaining stones (80 – 85% of all stones), which are associated with or formed from a variety of metabolic or environmental disturbances, stone composition is helpful but not conclusive for diagnosis of the underlying disease.

Radiologic Appearance (Kidneys, Ureter and Bladder)

Most stones can be detected by radiograph of the kidneys, ureter, and bladder (KUB) alone. Radiopaque stones include those containing calcium oxalate, calcium phosphate, and infection stones (due to their component of carbonate apatite). Cystine stones are also radiopaque, though less dense. Radiolucent stones include those composed solely of uric acid, 2,8-dihydroxyadenine, triamterene, xanthine and silica. Uric acid may have a faint radiopacity because of the incorporation of calcium salts. The morphologic appearance of radiopaque stones may provide clues to their mineral composition or to the underlying process. Cystine stones are moderately dense and have a homogeneous appearance. Struvite stones are more dense but also tend to have a rounded appearance. Cystine and infection stones may reach staghorn size. Calcium oxalate stones often have a dense, spiculated appearance.

Cortical nephrocalcinosis suggests the diagnosis of primary hyperoxaluria. Medullary nephrocalcinosis is encountered in distal RTA and primary hyperparathyroidism.

Other imaging modalities such as intravenous urography (IVP) or ultrasonography are useful in detecting radiolucent stones, anatomic abnormalities (e.g. medullary sponge kidney), or complications produced by a stone (e.g. obstruction) [116].

Blood Tests

A multichannel screen of venous blood should be performed to identify primary hyperparathyroidism (high serum calcium concentration), gouty diathesis (hyperuricemia), complete distal RTA (hypokalemia, low CO_2, and hyperchloridemia), or hypophosphatemic absorptive hypercalciuria (hypophosphatemia due to phosphate renal leak). In addition, serum creatinine and BUN are helpful to assess renal function.

Urinalysis and Urine Culture

A fresh spot urine sample should be cultured for urea-splitting organisms (suggestive of infection stones) and examined for pH (with an electrode pH). Low urinary pH (< 5.5) suggests gouty diathesis and high pH (> 7.5) is compatible with infection stones. A qualitative cystine test should be performed on the urine sample, using the cyanide-nitroprusside test, in which a purple-red color after addition of sodium cyanide and sodium nitroprusside suggests that cystine excretion exceeds 75 mg/L [117]. A false-positive test may be obtained in patients with homocystinuria and acetonuria. Follow-up quantitative analysis showing 24-hour urinary cystine > 250 mg/g creatinine confirms diagnosis. Identification of a particular crystal type in the urinary sediment is compatible with, but not

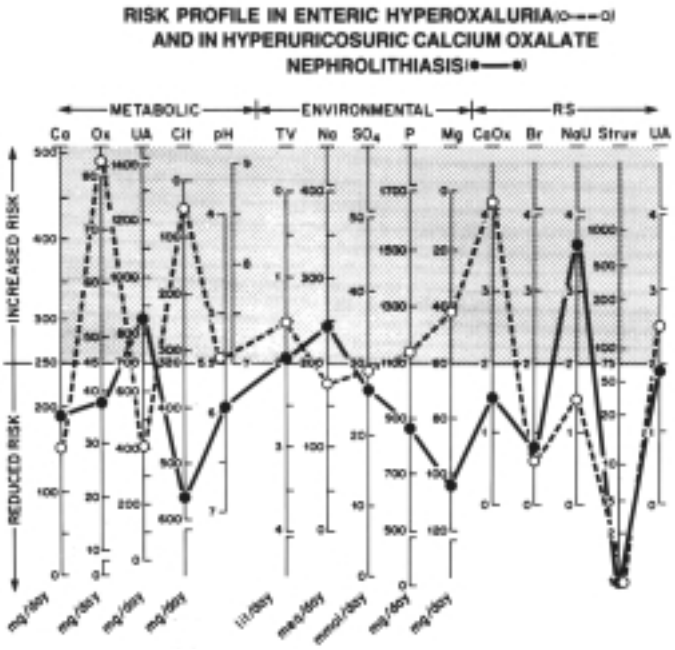

Figure 9. Graphic display of urinary risk factors in patients with enteric hyperoxaluria and with hyperuricosuric calcium oxalate nephrolithiasis. From [Pak CYC, Skurla C, Harvey J 1985 Graphic display of urinary risk factors for renal stone formation. J Urol *134:* 869], figure 3).

diagnostic of, that type of nephrolithiasis. Thus, crystalluria itself is not a pathologic finding.

24-hour Urine for Urinary Risk Factors

This simplified approach takes advantage of commercially-available stone risk analysis. The technique was first developed in our laboratory at Dallas [118]. A 24-hour urine collection kit, containing a volume marker and appropriate preservatives, is provided by the physician to the patient. After obtaining a 24-hour urine sample while the patient is kept on random diet and fluid intake, 2 30 mL aliquots are sent via regular mail to a central laboratory. The laboratory then calculates the total volume from the dilution of the volume marker and analyzes urinary constituents. Risk factors are categorized into 3 groups: metabolic risk factors (calcium, oxalate, uric acid, citrate, and pH), environmental risk factors (total volume, sodium, sulfate, phosphorus, and magnesium), and physicochemical risk factors (saturation of urine with respect to stone-forming constituents calculated from metabolic and environmental factors). Results are displayed graphically or in a tabular format.

A sample stone risk profile as originally reported in 1985 is shown in Figure 9. To provide a visual display of all available data in a single report, each risk factor is assigned a vertical line with linear or logarithmic scales. A horizontal line intersecting each vertical scale at the approximate midpoint represents the upper or lower normal limit. The direction of increasing values is appropriately adjusted, so that values below the horizontal line represent normal values (reduced risk)

Table 8. Dietary Modifications for Diagnostic Assessment

Finding in 24-h urine (on random diet)		*Modification (1 week)*
Total volume	< 2 L/day	Increase fluid ingestion
Sodium	> 200 mEq/day	Sodium restriction
Oxalate	> 45 mg/day	Oxalate restriction
Calcium	> 250 mg/day	Calcium restriction (moderate)
Sulfate	> 30 mg/day	Restriction of animal proteins
Uric acid	> 600 mg/day	Restriction of animal proteins

and those above the line represent abnormal values (increased risk). In this case, samples of two patients are displayed. A patient with small bowel disease (dotted line) had hyperoxaluria (from increased oxalate absorption), hypocitraturia and low urinary pH (from acquired metabolic acidosis), low urine volume (from diarrhea), and low urinary magnesium (from malabsorption). As a consequence, urinary saturation of calcium oxalate and uric acid was higher than normal, accounting for the susceptibility of patients with ileal disease to form stones of calcium oxalate and uric acid. The other patient (continuous line) had hyperuricosuria as the sole metabolic abnormality. Urinary sodium was high from dietary salt abuse. There was relative supersaturation of monosodium urate. The first case is a typical patient with enteric hyperoxaluria, whereas the latter is a patient with hyperuricosuric calcium oxalate nephrolithiasis.

The accuracy of urine collection could be assessed from urinary creatinine values and body weight. In a carefully studied population on a metabolic dietary regimen in whom the accuracy of urine collection was ensured, the mean urinary creatinine in men was 22.1 ± 4.7 mg/kg, whereas it was 17.2 ± 3.8 mg/kg in women. Thus, a value substantially below these figures would indicate undercollection, and a value far exceeding these numbers would suggest overcollection [108].

After obtaining a full stone risk analysis in a urine sample collected on random diet, the next step is to impose a short-term dietary modification (minimum one week) (Table 8) [119]. Fluid intake should be increased at least to ten 10-ounces glasses per day if urine volume is < 2 liters on the stone risk analysis. Salty foods and table salt should be avoided if urinary sodium > 200 mEq/day. Oxalate restriction should be imposed (avoidance of nuts, spinach, chocolate, tea, and vitamin C). Calcium intake should be restricted (avoidance of dairy products and spinach, for diagnostic purpose only) if there is hypercalciuria. Servings of meat products should be limited when there is hyperuricosuria, or if urine sulfate is high.

The last step in this simplified diagnostic protocol for nephrolithiasis is to obtain a 24-hour urine collection while the patient is on a temporary dietary modification. A limited analysis could be performed, involving 7 constituents: calcium, oxalate, uric acid, citrate, pH, total volume, and sodium. The differences in values between the full and the abbreviated analysis (random and modified diet) represent changes imposed by dietary influences.

The work-up described above should allow differentiation of most causes of stones (absorptive hypercalciuria, renal hypercalciuria, hyperuricosuric calcium oxalate nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis). However, for the simplified ap-

proach to the medical management of nephrolithiasis to be described, only the following differentiations are necessary. First, separate uncomplicated stone disease from other stone disease (Figure 8). The former, constituting the majority of patients with stones, is characterized by calcium oxalate or calcium apatite stones, normal serum calcium and uric acid, and the absence of chronic UTI, bowel disease, or marked hyperoxaluria. Other stone disease would comprise patients with primary gout with hyperuricemia, infection stones, cystinuria, distal RTA, primary hyperparathyroidism, and primary or enteric hyperoxaluria.

Categorization of Uncomplicated Stone Disease

Once patients with uncomplicated stone disease have been identified, an additional diagnostic separation is necessary in this group for purposes of medical treatment. From the 24-hour urine calcium obtained previously, uncomplicated calcium stone disease is separated into normocalciuric and hypercalciuric subgroups (Figure 8). The normocalciuric subgroup would be composed of hyperuricosuric calcium oxalate nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis, gouty diathesis, and hypomagnesiuric calcium oxalate nephrolithiasis, all presenting with normal urinary calcium. The hypercalciuric subgroup comprises absorptive and renal hypercalciuria, and dietary hypercalciuria.

Most practicing physicians should be able to identify the groups without difficulty.

A Simple Approach to Medical Treatment

Conservative Management

All patients with nephrolithiasis should be offered a conservative treatment program, similar to dietary modifications imposed for diagnostic purposes (Table 8).

Fluid intake should be sufficient to assure a urine level ≥ 2 L/day [80]. Adequate hydration in the absence of any other treatment has been recently proved to decrease stone formation by as much as 55% during a 5-year follow-up [79]. The type of liquid is generally of less concern than the volume; exceptions include the avoidance of tea in hyperoxaluria and excessive milk in absorptive hypercalciuria. Fluids are most valuable if they are distributed throughout the day. Patients also should be encouraged to measure the urine volume regularly (once every 2 – 3 months) to ensure its adequacy.

Traditionally, calcium restriction has been the mainstay of stone prevention. However, this measure may be ineffective in normocalciuric patients and may cause negative calcium balance and bone loss. Our practice is to recommend a moderate restriction of dietary calcium (limit dairy products to one serving/day) only in hypercalciuric patients with normal bone density, and not to restrict calcium in others.

Other dietary modifications have already been explained. Conservative management alone may be necessary in patients with mild disease, those with a single episode, or those without metabolic disturbance. Conservative management should always accompany specific drug therapies in patients with more severe recurrent disease, since it will improve the control of stone risk factors and may allow the use of a lower dose of recommended drugs. In severe stone disease or recurrences

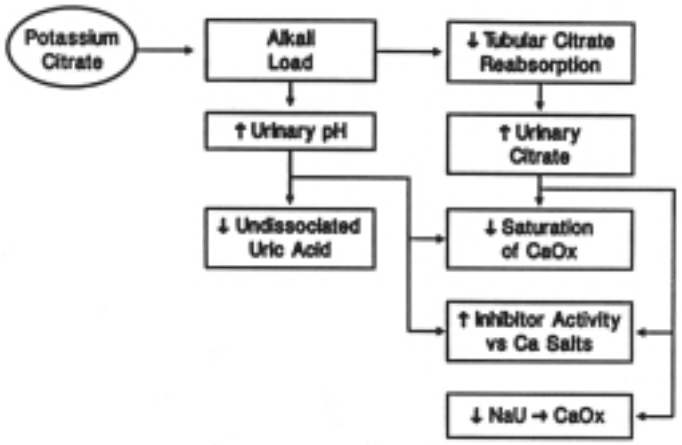

Figure 10. Physicochemical action of potassium citrate. (From Pak CYC 1990 Hypocitraturic calcium nephrolithiasis. In: Resnick MI, Pak CYC. (eds): Urolithiasis, WB Saunders, Philadelphia, figure 6 – 4, p 98, with permission).

despite conservative management, drug treatment is indicated.

Treatment of Uncomplicated Stone Disease

The simplified approach advocates the use of only 2 drugs as initial options in uncomplicated calcium stone disease (Figure 8). The normocalciuric subgroup would be prescribed potassium citrate (Urocit-K) alone. The hypercalciuric subgroup would be given thiazide and potassium citrate.

The rationale for potassium citrate in uncomplicated normocalciuric stone disease is shown in Figure 10. Potassium citrate increases citrate excretion by providing an alkali load [74, 75]. The induced rise in urinary citrate should inhibit the crystallization of calcium oxalate and calcium phosphate, not only in hypocitraturia, but also in the presence of other derangements such as hyperuricosuria. In addition, potassium citrate raises urinary pH, reducing the propensity for uric acid stone formation. The complication of calcium stone should be inhibited as well from the impaired urate-induced calcium oxalate crystallization. A placebo-controlled randomized trial has validated the efficacy of potassium citrate in uncomplicated stone disease with normocalciuria [120]. Among patients treated with potassium citrate, 72% had no further stone formation during a follow-up of 3 years, compared with 20% in the placebo group. Moreover, for those in the treatment group who still formed stones, the stones developed at a lower rate than before treatment.

Potassium citrate (Urocit-K) is available as wax matrix tablets, containing 5 or 10 mEq of citrate per tablet. It is also available as a liquid, powder or syrup combining potassium citrate and citric acid (PolyCitra-K); the powder and syrup are mixed with water before ingestion. The wax matrix tablet formulation has been shown to produce less variability in the level of urinary citrate throughout the day [121]. The customary dose of potassium citrate is 20 mEq twice daily; the dose should be adjusted based on urinary citrate [74, 75]. Contraindications for its use are hyperkalemia or predisposing conditions to hyperkalemia (type IV RTA, concomitant use of potassium-sparing diuretics, adrenal insufficiency), renal failure

(GFR < 40 mL/min), active peptic ulcer disease, UTI or obstruction.

The rationale for the combined use of thiazide with potassium citrate in hypercalciuric patients with uncomplicated stone disease is based on following considerations. Thiazides are unique among diuretics in reducing urinary calcium excretion. Thiazides act directly on the distal convoluted tubule to augment calcium reabsorption, and indirectly at the proximal convoluted tubule secondary to volume depletion [122]. They are widely used in the management of hypercalciuric nephrolithiasis [123]. However, thiazide-induced hypokalemia may lead to intracellular acidosis, which provokes hypocitraturia and may thereby attenuate the beneficial hypocalciuric effect of therapy on renal stone formation [123, 124]. Potassium chloride supplementation may prevent hypokalemia and hypocitraturia. In the management of stone disease, potassium citrate is preferable because it can not only avert hypokalemia, but also raise urinary citrate, an important inhibitor of stone formation [124, 125]. Amiloride has been shown to potentiate the hypocalciuric effect of thiazides while reducing the associated hypokalemia; however, amiloride has no effect on urinary citrate [126]. Therefore, the combination of a thiazide and potassium citrate is preferred.

The recommended doses of thiazides in an average adult patient are trichlormethiazide 4 mg daily, chlorthalidone 50 mg daily, hydrochlorothiazide 25 mg twice daily, or bendroflumethiazide 2.5 mg twice daily. Long-acting agents are preferable, since compliance may be better. Potassium citrate should be added in doses of 15 – 20 mEq twice daily to prevent thiazide-induced hypokalemia and hypocitraturia. A modest sodium restriction is advisable in conjunction with thiazide therapy because excessive sodium intake attenuates the hypocalciuric effect of the drug [127].

Future Treatment of Uncomplicated Stone Disease After Relapse

Some patients may be intolerant of, or may not respond to potassium citrate therapy. Moreover, potassium citrate does not correct magnesium loss in long-term thiazide therapy or hypomagnesiuria that is encountered in 7% of patients with recurrent calcium nephrolithiasis [6]. Potassium-magnesium citrate (K_4MgCit_2 or K-Mag), a new drug under development by the Dallas group, may overcome these problems. Compared to Urocit-K at the same dose of potassium, K-Mag causes a more prominent rise in urinary citrate and pH [128] and a greater inhibition of the propensity for the crystallization of uric acid and calcium oxalate [129]. A recent placebo-controlled, randomized trial indicated that K-Mag is highly efficacious in inhibiting calcium stone formation during a 3-year follow-up. The relative risk of stone-free rate (K-Mag/placebo) was 0.15 (95% confidence interval, 0.05 to 0.44) [7]. Finally, in a randomized, controlled comparison of gastrointestinal tolerance of K-Magvs.Urocit-K, the former drug appeared to be better tolerated [130].

Thiazide may not be effective in all patients with hypercalciuric nephrolithiasis. There may be an attenuation or loss of hypocalciuric action after ≥ 2 years of thiazide treatment because of its inability to correct the underlying intestinal hyperabsorption of calcium [131]. Thiazide may cause hypokalemia, volume depletion, impotence, hyperuricosuria, and hyperuricemia.

Slow-release neutral potassium phosphate (UroPhos-K), a new drug being developed by our group at Dallas, may obviate the problem of thiazide therapy in the future. Its slow release minimizes gastrointestinal side effects, unlike conventional phosphate preparations. It causes a small sustained rise in serum phosphate and a slight parathyroid stimula-

tion within the normal range. Thus, there is suppression of calcitriol synthesis. Calcium absorption is reduced about 50% by inhibition of calcitriol synthesis as well as from the binding of calcium by phosphate in the intestinal tract. Moreover, UroPhos-K increases urinary citrate (from the alkali load) and pyrophosphate (from the rise in orthophosphate excretion), 2 important inhibitors of calcium stone formation, and inhibits crystal agglomeration of calcium oxalate [132].

UroPhos-K treatment in patients with absorptive hypercalciuria produced a substantial decline in the urinary saturation of calcium oxalate at 3-month follow-up [132]. The saturation for calcium phosphate did not change, because the rise in urinary phosphorus was compensated for by a decline in urinary calcium. Unlike thiazide, the hypocalciuric effect remained over 4 years of treatment. This effect is probably a combination of reduced intestinal calcium absorption, reduced skeletal calcium mobilization, and a possible augmented renal calcium reabsorption [133].

Thus, K-Mag and UroPhos-K promise to be useful alternatives or potentially superior agents to be used in lieu of thiazide and potassium citrate, especially in relapse.

Treatment of Other Stone Disease

Treatment of conditions other than uncomplicated calcium stone disease is well established (Figure 8).

If uric acid stones are found, gouty diathesis or conditions causing undue urinary acidity should be suspected. Potassium citrate is the treatment of choice for gouty diathesis. A dosage of 30 – 60 mEq/day in divided doses raises the low urinary pH (< 5.5) to the desired range of 6.0 – 7.0 [134]. Although sodium alkali is as effective as potassium citrate for prevention of uric acid stone formation by increasing urinary pH, it may induce the formation of calcium stones by its hypercalciuric action [135].

The mainstay of managing infection stones is surgical removal of the stone and eradication of urea-splitting organisms. Antibiotics are given before and after surgery to reduce recurrence. Acetohydroxamic acid, a urease inhibitor, reduces urinary saturation of struvite by preventing the formation of ammonium and hydroxyl ions. It may prevent stone growth and sometimes cause dissolution of existing stones. Unfortunately, its use is associated with significant side effects (hemolytic anemia, thrombophlebitis, and neurological disorders) [101].

In patients with cystine calculi and moderate cystinuria (250 – 500 mg/day), high fluid intake and potassium citrate (30 – 60 mEq/day in divided doses) is recommended to maintain urinary pH at a high normal range of 6.5 – 7.0. When further therapy is necessary, the addition of sulfur-chelating agents such as alpha-mercaptopropionylglycine (MPG or Thiola) or penicillamine will reduce cystine excretion. These agents act by complexing cysteine, the monomeric form of cystine. Both drugs are associated with frequent and sometimes severe side effects, including nephrotic syndrome, dermatitis, and pancytopenia. Penicillamine is administered in a daily dose of 1 – 2 g in 3 or 4 divided doses. Thiola (800 – 2000 mg/day in 3 or 4 divided doses) is preferred, because it has a lower toxicity profile than penicillamine [104].

Patients with brushite stone have a high recurrence rate. Distal RTA or primary hyperparathyroidism, the most frequent secondary causes, should be ruled out [100, 136]. If there is no evident secondary causes, these patients may be treated according to the guidelines for uncomplicated stone disease.

If hypercalcemia is found, work-up for primary hyperparathyroidism should be under-

taken. Parathyroidectomy is the optimal treatment for the nephrolithiasis associated with primary hyperparathyroidism. A medical approach with phosphates or estrogens (in postmenopausal women) should be used only when parathyroid surgery cannot be undertaken [137].

Allopurinol treatment should be considered for anyone with hyperuricemia because of the risk of gouty arthritis. It is administered at a dosage of 300 mg/day. Side effects are rare and include a skin rash and a reversible elevation of liver enzymes. In the event of a rash, the drug should be discontinued immediately because it may progress to Stevens-Johnson syndrome.

Finally, the finding of marked hyperoxaluria mandates a search for primary or enteric hyperoxaluria. The established treatment regimen for primary hyperoxaluria is orthophosphate, 1.5 – 2.5 g of phosphorus per day in 3 or 4 divided doses, and pyridoxine 100 mg twice a day. Orthophosphate reduces urinary calcium and augments urinary pyrophosphate. If given in a neutral form, it increases citrate excretion. Thus, the urinary saturation of calcium oxalate is reduced, and the inhibitor activity against calcium oxalate crystallization may be augmented. Pyridoxine may reduce urinary oxalate excretion by reduction of endogenous oxalate synthesis in some patients. Potassium citrate may be a useful therapeutic option in lieu of orthophosphate. Patients should be maintained on these programs as long as complications are controlled and renal function remains stable. If this is not the case, then planning for renal and/or liver transplant is necessary [89, 91].

Specific therapies to correct fat malabsorption such as a gluten-free diet (celiac sprue), pancreatic enzyme replacement (pancreatic insufficiency), or the use of antibiotics (bacterial overgrowth) may be required in some cases of enteric hyperoxaluria. In patients with significant fat malabsorption, a low-fat diet with medium-chain fatty acid supplementation should be instituted to minimize steatorrhea. Medical therapy to prevent stones in this condition is directed at decreasing oxalate absorption and correcting associated metabolic complications. Calcium citrate (400 mg of calcium with meals) may be useful to decrease urinary oxalate by binding oxalate in the intestinal tract. It may raise urinary citrate and pH by providing an alkali load. Careful monitoring of urinary calcium and oxalate should be routine. Magnesium supplements act via an identical mechanism: binding free oxalate in urine. Cholestiramine does not cause a sustained reduction in oxalate excretion. Low urinary pH and hypocitraturia can be treated with potassium citrate 40 – 60 mEq/day in divided doses. Severe cases may require larger doses up to 120 mEq/day. K-Mag, which provides citrate as well as magnesium, should be the logical therapeutic option in enteric hyperoxaluria to correct associated metabolic disturbances [89, 138].

Conclusion

This chapter presents a simplified approach to stone disease. First, obtain a full analysis of urine for stone risk factors to identify environmental or metabolic disturbances. Second, obtain an abbreviated stone risk profile after a dietary modification. Differentiate between patients with uncomplicated calcium stone disease and patients with other stone disease. In the former group, separate patients into hypercalciuric and normocalciuric subgroups. In those with normal urinary calcium, apply potassium citrate therapy. In those with hypercalciuria, treat with thiazide and potassium citrate. For those with multiple relapses, new drugs are under development, particularly potassium-magnesium citrate and slow-release neutral potassium phosphate.

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Evaluating Solid and Cystic Lesions of the Kidney

Thomas H. Waid

The presentation of cystic and solid renal lesions differs today from that of 25 years ago. The classic triad of renal cell carcinoma (RCC), flank pain, hematuria, and palpable mass represents a minority of presentations, albeit microscopic hematuria remains an almost universal, often early sign. Because of advances in computerized tomographic imaging technology, detection of incidental tumors serendipitously discovered during screening or other diagnostic examinations is increasing. The paradigm of diagnosis based on clinical presentation followed by excretory urogram (intravenous pyelogram (IVP)) to demonstrate a mass, ultrasound to differentiate solid from cystic lesions and then cyst puncture or angiography has succumbed to computed tomography (CT) and magnetic resonance imaging (MRI). Arteriography, cyst aspiration for cytology and fine needle aspiration biopsy (FNA) are rarely necessary and diagnostic percutaneous renal biopsy almost never needed.

The purpose of this chapter is to characterize the renal mass lesions, cystic and solid, benign and malignant, encountered by the nephrologist and internist and to act as a guide for evaluation of the lesions and possible referral to a urologist for further evaluation and/or operation.

Systematic Evaluation of Renal Mass Lesions

Patients presenting with complaints of gross hematuria, flank pain, or fullness, or those who have persistent microscopic hematuria warrant an evaluation for mass lesions of the urinary tract, particularly if smokers. In the past, renal masses remained undetected until they grew to be quite large, producing local symptoms. However, the routine use of ultrasonography and CT allows earlier detection.

Excretory Urography (Intravenous Pyelography)

When a patient presents with clinical symptoms, intravenous excretory urography, despite its lack of sensitivity and specificity, remains the initial study of choice. It is an anatomic as well as a physiologic study with a time-honored role in evaluating hematuria; however, small masses, solid or cystic, may be missed. The urogram can establish the presence of a mass; it cannot indicate what the nature of the mass might be. Radiographic signs such as distortion, elongation, and amputation of the calices can occur with renal

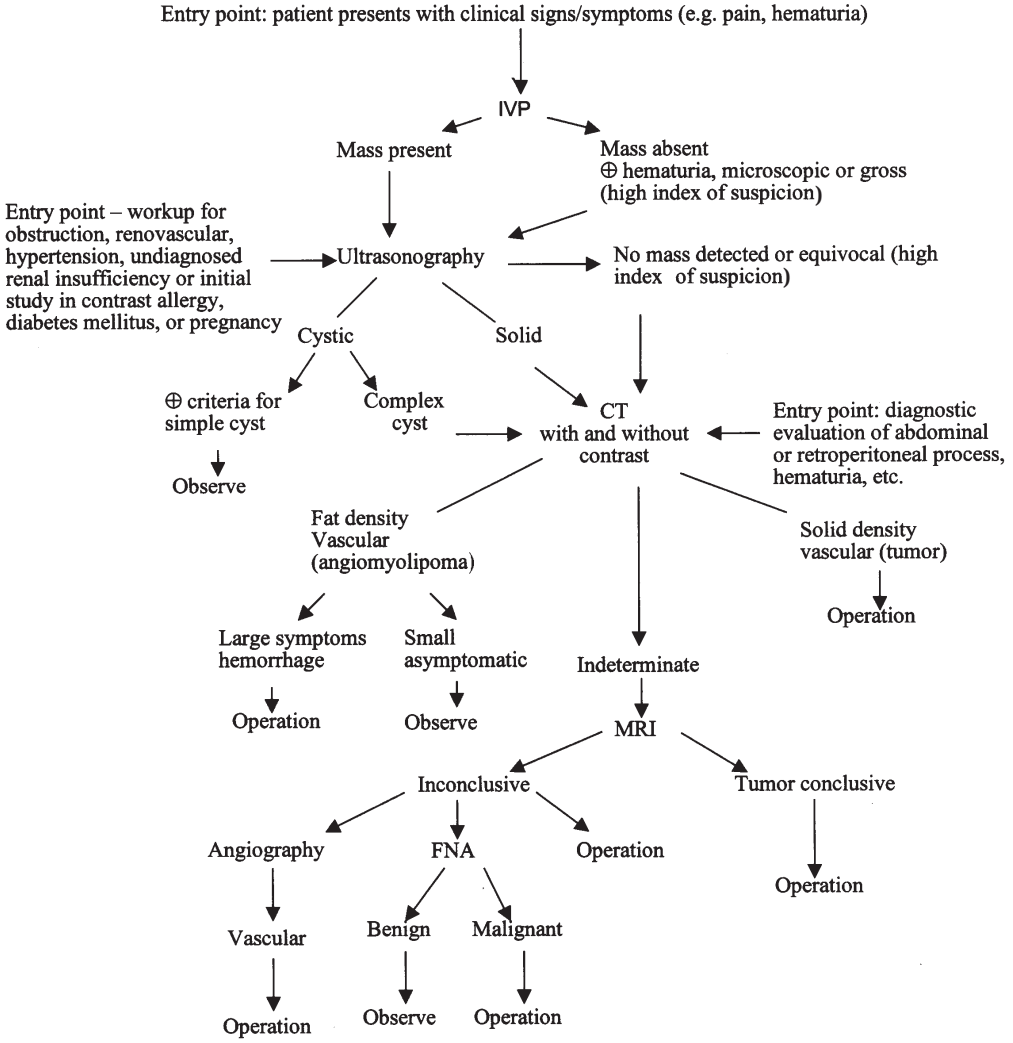

Figure 1. Algorithm for evaluating renal masses with 3 entry points: 1) IVP (urography) for clinical signs and symptoms; 2) sonography for evaluation of other clinical conditions or if the patient is contrast allergic, diabetic or pregnant; 3) CT for evaluation of other abdominal or retroperitoneal processes or hematuria. Entry point: patient presents with clinical signs/symptoms (e.g. pain, hematuria).

tumors or cysts. The deformity of the calices, infundibula, and pelvis can be identical, except that cysts do not commonly amputate the calices, whereas tumors do [1]. Both cysts and tumors can likewise distort the kidney capsule, giving it an irregular outline on urographic imaging; however, so can an area of compensatory hypertrophy [1]. Truly, excretory urography continues to occupy an important role in initial screening, despite the availability of newer imaging techniques. Additionally, solid and cystic renal masses may be discovered when ultrasonography or CT has been employed in other diagnostic en-

deavors. This may change the starting point of the algorithm and excretory urography may be unnecessary. A systematic diagnostic approach to the renal mass lesion is seen in Figure 1.

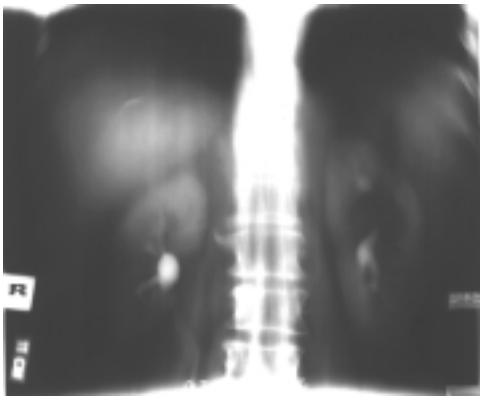

Figure 2a. Benign simple renal cyst. a) 71 yo white female with squamous cell carcinoma of the rectum. An IVP was performed to locate the ureters before surgery. It displayed a normal right kidney and a lucent filling defect in the left kidney with pressure deformation of the collecting system. b) Ultrasound reveals a sharply demarcated, echo-free mass located in the upper pole of the left kidney. The walls are thin. There are no calcifications or internal echoes, and enhanced sound transmission through the cyst is evident.

Ultrasonography

Ultrasonography is the study most widely used to determine whether a mass lesion demonstrated on excretory urography is solid or cystic. It may also be used as an initial screening technique in patients with chronic renal failure, diabetes mellitus (DM), pregnancy, or contrast allergy [2]. If a mass fulfills all the strict criteria for a simple cyst, such as a round or oval shape with through transmission without acoustic shadows off of any internal echoes and a strong posterior wall, there is no need for further workup in the otherwise asymptomatic patient (Figure 2a, b). Failure to fulfill these criteria warrants further evaluation by CT. Percutaneous cyst puncture and aspiration cytology have largely been abandoned because the results were frequently nondiagnostic except in simple benign cysts, which can be classified sonographically or by CT [3]. Finally, masses seen on urography may not be detected by ultrasound if they are isoechoic with the renal parenchyma. Examples are fetal lobulation and a hypertrophied column of Bertin. Whereas radionuclide scanning was used in the past for imaging these structures, contrast-enhanced CT is now the preferred test.

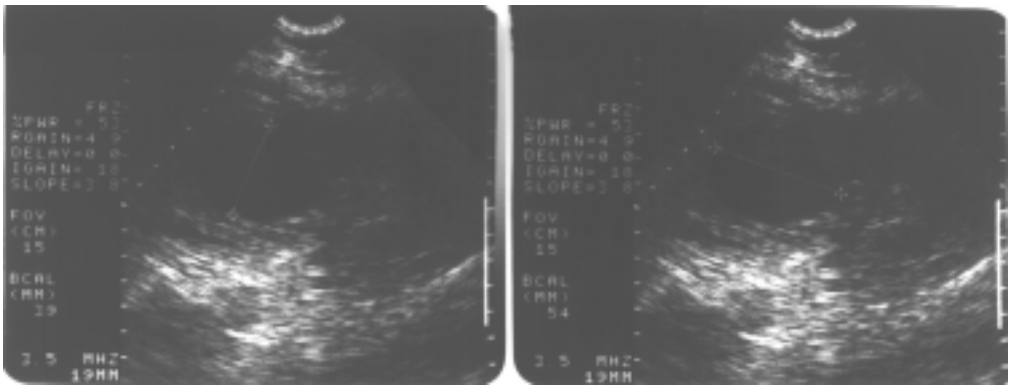

Figure 2b. Benign simple renal cyst. b) Ultrasound reveals a sharply demarcated, echo-free mass located in the upper pole of the left kidney. The walls are thin. There are no calcifications, or internal echoes, and enhanced sound transmission through the cyst is evident.

Computed Tomography (CT)

Presently, CT scanning has assumed the preeminent role in imaging renal masses and complex cysts. CT scanning, with and without oral and intravenous contrast, is more sensitive in detecting small renal masses, the presence of fat within tumors, the overall density of the mass, and the extent, if any, of retroperitoneal involvement. As stated above, CT scanning has essentially eliminated cyst puncture and aspiration cytology and has all but eliminated arteriography, with a few notable exceptions. The limitations of CT are few, but it is important to remember that differentiation of atypical angiomyolipomas, complex cystic masses, and inflammatory or infectious masses from malignant solid tumors may not be possible. Under these circumstances, further imaging with MRI, arteriography, or FNA cytology may be indicated, albeit rarely.

Magnetic Resonance Imaging (MRI)

MRI as an imaging tool offers some advantages over CT and is especially useful when the use of intravenous contrast is contraindicated. MRI is useful in evaluating vascular and adjacent organ invasion. Enhancement with gadolinium contrast allows detection of renal masses of < 3 cm in size. Because of its expense, it remains an adjunct to CT.

Arteriography

Arteriography remains as a useful test in the evaluation of indeterminate renal masses. It is useful when nephron-sparing surgery is being considered, because it best defines the blood supply to the tumor and normal parenchyma. Digital subtraction angiography in combination with CT has been advocated as a suitable replacement for the more invasive and risky arteriogram, and appears to provide acceptable anatomic definition [4].

Solid and Cystic Masses

Whenever a renal mass is encountered on an excretory urogram or incidentally during sonography or CT, the immediate question is whether it is solid or cystic. Both types of lesions may be benign or malignant. Some may be characterized radiographically and need only be followed at specified intervals, whereas others require further evaluation and/or surgical removal.

Solid renal mass lesions that are evident on urography, sonography, and CT are generally upper urinary tract and retroperitoneal neoplasms. They may be benign or malignant and are listed in Table 1. Individual lesions and their evaluation will be discussed below. It is critical that the solid mass be characterized as malignant or benign; modern diagnostic technology has decreased to < 10% the number of masses remaining indeterminant before definitive therapy. Multiple solid tumors may be associated with multiple renal cysts in three conditions: chronic renal failure with or without dialysis, von Hippel-Lindau syndrome (vHL), and tuberous sclerosis (TS).

Cystic lesions of the kidney remain both a commonly encountered and complicated condition. Benign renal cysts still account for 55% of renal masses first seen on excretory urography, and can be defined by ultrasonography or CT [5]. Although modern imaging techniques usually allow diagnosis, the morphology can be quite confusing, and complicated cystic lesions can present dilemmas in

Table 1. Classification of Urinary Tract and Retroperitoneal Neoplasms

Renal - Primary Benign	*Retroperitoneal*
Adenoma	Lipoma benign
Angiomyolipoma-hamartoma	Lymphoma → malignant
Fibroma	
Hemangioma	Sarcoma → malignant
Juxtaglomerular tumor	
Leiomyoma	
Lipoma	
Oncocytoma	
Renal – Primary Malignant	*Renal – Secondary Malignant*
Renal cell carcinoma – hypernephroma	Retroperitoneal sarcoma
Urothelial carcinoma	Carcinoma – spread from following:
Transitional cell	Pancreas, colon (direct spread);
Squamous cell	lung, breast, GI tract (hematogenous spread)
Adenocarcinoma	
Sarcoma	
Adult Wilms' tumor	Lymphoma, leukemia and myeloma (plasmacytoma)

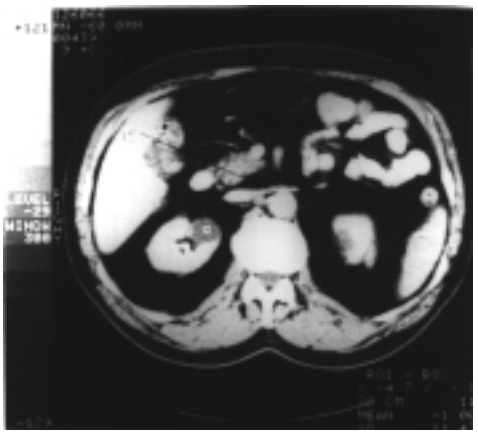

Figure 3. Benign renal cyst. The patient, a 50 yo white male, presented with hematuria and no other symptoms. CT shows an oval-shaped cystic structure. The kidney is not enlarged, and there is no distortion of the renal outline. The density of the mass is uniform with homogenicity of contents and overall less dense than the renal parenchyma. The incidence of simple cysts is high, occurring in > 50% of adults over 50 yo.

diagnosis and management. Fortunately, the work of Bosniak has provided some clarification and classification of cystic lesions [3, 6 – 8]. The Bosniak classification, first proposed in 1986, places cystic renal lesions into 4 categories (Table 2). As previously described, a round or ovoid lesion with through sonography without internal echoes and strong acoustic shadows off the back wall requires no further evaluation. However, more complex lesions require CT. Most category I, minimally complicated category II, obvious category III, and category IV lesions can be diagnosed with enhanced scans. There are some complicated category II lesions and equivocal category III lesions that still present a diagnostic dilemma, especially when surgical exploration is being contemplated [6]. Examples of benign cysts are seen in Figure 2a and b and Figure 3. A more complicated cyst is seen in Figure 4.

The technique of CT scanning is also important, especially when renal cysts are dis-

Table 2. Bosniak Classification of Cystic Lesions of the Kidney

- Category I: Benign – do not require operation
  Simple, uncomplicated, benign cysts
  Round or ovoid with thin walls
  No internal septae or calcification
  Fluid in cysts with attenuation of clear fluid
- Category II: Benign but not simple – do not require operation, but may require 6 month follow-up
  Slightly more complicated cysts
  One or more septae in cyst
  Thin areas of calcification in cyst wall or septae
  Fluid in cyst with higher attenuation than clear fluid
- Category III: Some characteristics of cystic neoplasms – operation required
  More complicated cyst with thickened wall or septae
  Thickened areas of calcification
- Category IV: Clearly malignant lesions – operation required
  In addition to Category III criteria, these lesions have solid elements that enhance with contrast material

covered during abdominal scanning using intravenous and/or oral contrast where preliminary unenhanced scans are not available for comparison. In such a situation, scanning following bolus contrast administration is not done and the tubular nephrogram phase is missed. Additionally, thin (5 mm) sections, often needed for high resolution of more complicated cysts, are often unavailable. In such cases, if the original study is inadequate, it needs to be repeated, both unenhanced and enhanced, with attention to the tubular nephrogram phase and with thin sections through the renal parenchyma. One should not attempt to classify cysts with inadequately performed examinations [9, 10].

In a recent presentation by Levy et al. at the Radiological Society of North American, December 1996, the Bosniak classification was reported to display a diagnostic accuracy of 100% in 88 patients with cystic renal lesions. All category I and category II lesions were benign; all category IV lesions were malignant, as were 46% of the category III lesions. Obviously, the classification can be very operator dependent, and the area of greatest diagnostic uncertainty arises between catego-

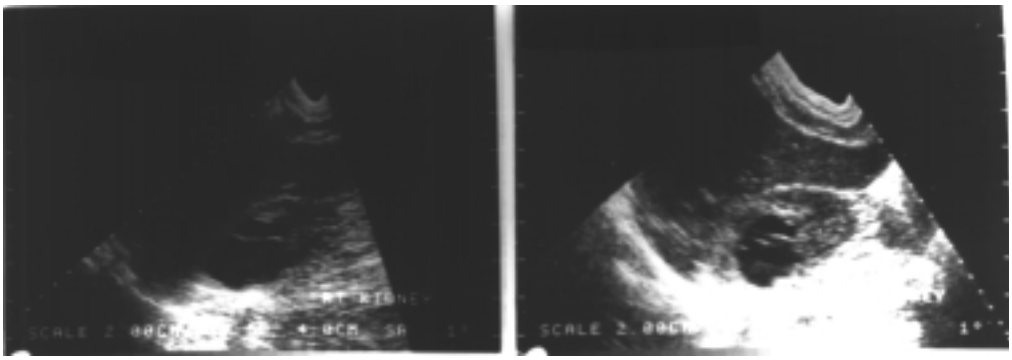

Figure 4. Multilocular cyst. This is a 34 yo white male with a 2 day history of right flank pain radiating to his right testicle. Evaluation for a kidney stone began due to his history and the presence of microscopic hematuria. An IVP revealed irregular calcified densities in the right pelvis and a 3 cm radiolucent area in the midportion of the right kidney. Ultrasound revealed a multilocular cyst with internal septae. CT was recommended and the patient was followed every 6 months.

ries II and III. Operator experience, CT technique, and use of other imaging studies such as MRI are all important in rendering a diagnosis, and clinical criteria may often be the deciding factor [11]. Clinical information such as patient age, history of infection, heart disease, hematuria, and lesion size are not only important in diagnosis, but also deciding between observation or exploration.

Acquired Renal Cystic Disease

Nephrologists should be especially aware of acquired renal cystic disease (ARCD) in their dialysis population. Approximately 45% of patients acquire multiple renal cortical cysts, with a 9% incidence of renal tumor development – 2500 times greater than the normal population. These patients may present with gross or new-onset microscopic hematuria. An enhanced CT scan should be done [12]. Rarely, the patients develop tumor-associated secondary erthyrocytosis, which may be masked by erythropoietin therapy. CT reveals contrast-enhancing solid renal masses among renal cysts. These masses may be single or multiple, unilateral or bilateral. There is a 6% rate of metastases in ARCD patients with renal tumors (0.54% of all patients with ARCD). The rate of tumor development correlates directly with the duration of chronic hemodialysis, with patients of < 3 years duration having a 43.5% incidence, increasing to 79.3% in those patients dialyzed > 3. Patients with chronic renal failure who do not require dialysis also have an increased propensity for developing renal cysts, as do patients on peritoneal dialysis. The latter patients do not seem to be predisposed to tumor formation [13]. Surgical resection of these masses is required, and since these tumors tend to be multiple and bilateral, native nephrectomy of both kidneys is recommended.

Benign Renal Tumors

Benign tumors of the kidney are common. Because they are usually asymptomatic, they are detected incidentally or at autopsy (Table 1). Abdominal sonography and tomography have uncovered these otherwise “silent” lesions which must be differentiated from malignant renal masses.

Adenoma

Renal cortical adenomas are the most common solid renal parenchymal lesions [14]. Adenomas are usually < 1 cm in size and are located exclusively in the cortex [15]. The etiology of the adenoma is unclear, although there is an association with smoking, dialysis, and arteriolar nephrosclerosis, as well as trisomy 7 and 17 and deletion of the Y chromosome [16, 17]. Adenomas are rarely symptomatic and paraneoplastic syndromes are not encountered. However, controversy persists in the literature as to the true clinical nature of these neoplasms. Indeed, there are suggestions that adenomas are not histologically distinguishable from carcinomas [18]. These tumors occur in the same 2:1 male:female ratio and are rarely found adjacent to a renal cancer, except in patients with acquired renal cystic disease or vHL. Because they are histologically indistinguishable from larger carcinomas, urologic oncologists recommend removal. Urologic referral of the patient with a small solid mass lesion thought to be adenomatous is important, because it is not possible to differentiate adenomas from carcinomas preoperatively based on size, symptoms, or radiographic imaging. These lesions should be considered malignant until proven otherwise.

Angiomyolipoma-Hamartoma

This benign tumorous lesion is a hamartoma of the renal parenchyma. It is unencapsulated and characterized by three histologic components: mature fat cells, smooth muscle, and abnormal vessels. The tumor may extend into the collecting system or perirenal fat, but there is no distant metastasis [19]. Hemorrhage and necrosis are common, and, very rarely, malignant degeneration of angiomyolipoma into a sarcoma with distant metastasis has been reported [20]. Finally, RCC and hamartoma may coexist in the same kidney.

Tuberous sclerosis (TS), an autosomal dominant condition affecting 1/150,000 live births, is associated in > 80% of patients with renal hamartomas. Brain gliosis, mental retardation, seizures, adenoma sebaceum of the face, submucosal fibromas, and hamartomas of the retina, lungs, liver, pancreas, bone, and kidney characterize the syndrome [22]. In these patients, the tumors are usually bilateral, small, and asymptomatic. Eighty percent of patients with renal hamartomas do not have TS. In these patients, usually women in the fourth to sixth decades, the lesions are larger, commonly unilateral, and present with symptoms caused by spontaneous rupture and retroperitoneal hemorrhage. Flank and abdominal pain occur in 50% of patients, combined with a palpable mass and hematuria. The diagnosis of hamartomas relies on the algorithm previously outlined. Intravenous urography with nephrotomography displays a solid mass in which malignancy cannot be established. Ultrasonography reveals high-intensity internal echoes suggesting fat (Figure 5). CT reveals the fat content (which has a negative density of -20 to -80 Hounsfield units), which is pathognomonic for hamartoma when it is observed in the kidney [23] (Figure 3a, b; Figure 6). Additionally, MRI may be used to aid in an equivocal diagnosis because of the high signal intensity of fat on T1-weighted images. Because all of the above diagnostic modalities rely on the proportion of fat within the tumor, rarely a small number of cases will remain uncertain. Only then should FNA biopsy be considered [24].

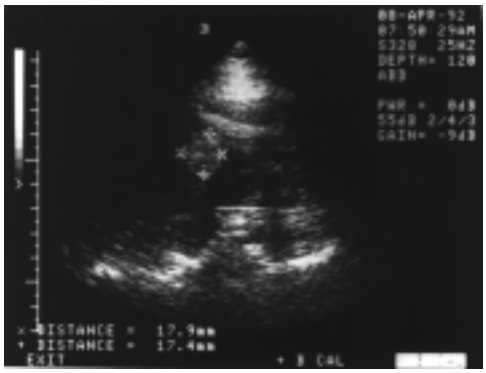

Figure 5. Hamartoma (angiomyolipoma). 68 yo white female referred for microscopic hematuria and proteinuria. History and physical exam were unremarkable. The urinalysis disclosed 2+ proteinuria and 5 – 10 RBC/HPF. IVP was read as being normal; however, abdominal ultrasound revealed a 2x2 cm echogenic focus with smooth margins and increased through transmission. Subsequent CT revealed an irregular 2x2 cm low-density lesion in the mid to lower pole of the left kidney without cystic features. MRI confirmed a 2 cm lesion with the intensity of fat on all pulse sequences.

The treatment of renal hamartomas depends on the size of the lesion. Asymptomatic tumors < 4 cm in size are followed by yearly sonograms. If the tumors are > 4 cm but asymptomatic, the elective follow-up may still be done yearly or semiannually. Fifty percent of these tumors will expand, requiring embolization or nephron-sparing surgery to prevent loss of renal parenchyma [25]. Finally, larger angiomyolipomas can hemorrhage into the kidney and/or retroperitoneum with life-threatening sequelae. In such cases, radical nephrectomy is the treatment of choice, although partial nephrectomy may be considered if the patient is known to have an angiomyolipoma preoperatively.

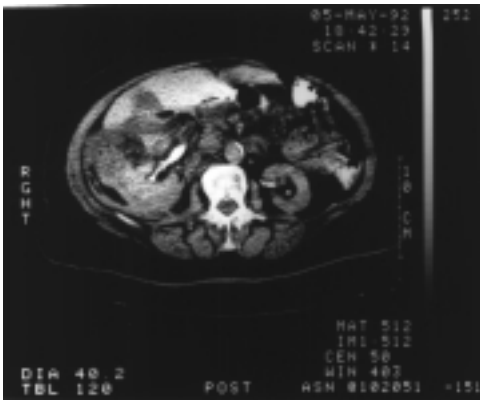

Figure 6. Hamartoma (angiomyolipoma). 70 yo white female with acute onset of right flank pain and hypotension. Emergent CT revealed a high density collection in the right perinephric space extending into the anterior and posterior pararenal spaces consistent with acute hemorrhage. There is fat density at the epicenter of the hemorrhage. This patient then had angiography, which revealed a large feeding vessel to a hypervascular mass but without the arteriovenous shunting seen in RCC. Because of the acute hemorrhage and hemodynamic instability, an operation was performed.

Oncocytoma

This benign renal tumor was not identified until recently [26]. Oncocytomas account for 5 – 7% of all renal tumors, or about 750 cases yearly. Asymptomatic in nature and usually discovered incidentally, these tumors affect patients in the fifth decade, and there is a 2:1 male:female predominance. In the latter 2 aspects, oncocytomas are similar to RCC. Unlike RCC, there are few distinguishable clinical signs and symptoms. Fewer than 20% of patients develop hematuria and the paraneoplastic syndrome is absent. Unlike the hamartoma, there are no characteristic features on urography, sonography, or CT.

These tumors are usually solitary and unilateral, although bilateral and multilateral cases have been reported. Histologically, oncocytes are large, well-differentiated cells with intensely eosinophilic cytoplasm packed with mitochondria. They rarely display mitosis or invade adjacent structures, and although, the exact cellular origin is unknown, they resemble proximal tubular cells [27]. Oncocytomas containing only pure oncocytoma cells (grade I) are benign with no metastasis, and no deaths due to tumor have been reported. Metastases and death have been reported in 15% of patient with so-called grade II tumors, which likely represents mixed tumors with elements of renal adenocarcinoma present. Because pure oncocytomas can neither be characterized radiographically nor can RCC be eliminated by FNA, radical nephrectomy remains the treatment of choice [28, 29].

Other Benign Renal Tumors

The remainder of the benign renal tumors – fibromas, lipomas, leiomyomas, hemangiomas, and juxtaglomerular cell tumors – are rare. Fibromas vary in size, exist mainly in females, arise mainly in the medulla, and therefore constitute the most common benign tumor of mesenchymal origin. Most of these tumors are small, totally asymptomatic, and found at autopsy [30]. Lipomas are usually found in middle-aged females. They arise form the kidney capsule and are composed of mature adipocytes [31]. When the tumor is large, the diagnosis may be made by CT due to the attenuation of fat. Hemangiomas are uncommon, but may be responsible for hematuria of an undetermined cause. They are usually < 2 cm in diameter, and occasionally multiple and bilateral. Diagnosis is not confirmed by sonography or by CT, but angiography is helpful in this regard [32].

Leiomyomas tend to be < 1 cm in size and arise from the kidney capsule or renal vessels. The lesions rarely require treatment despite the common occurrence of multiple tumors.

They usually occur in young white females, and hematuria and suggestion of a flank mass are the most common clinical presentations [33]. Radiographic techniques cannot provide a definitive diagnosis. If an operation is needed, radical nephrectomy is the procedure of choice, unless an intraoperative diagnosis can confirm the benign process and allow a renal-sparing operation.

Juxtaglomerular cell tumors are rare benign renal tumors with < 40 cases reported. Because they secrete renin, the patient presents with severe systolic and diastolic hypertension, hypokalemia, metabolic alkalosis, and elevated plasma renin and aldosterone activity. Patients are usually young, 70% being < 25 years of age, and two-thirds are female [34]. CT is the most helpful imaging method, with angiography being useful as a means of excluding renovascular hypertension. Total or partial nephrectomy is curative. As with other mass lesions, the latter can be accomplished only when the benign nature of the mass can be established preoperatively or intraoperatively.

Primary Malignant Renal Tumors

The primary malignant tumors include renal cell carcinomas, transitional cell carcinoma of the renal pelvis and collecting system, and more rarely squamous cell and adenocarcinoma of the urothelium, sarcoma and adult Wilms tumor. RCC accounts for about 90% of primary renal tumors and transitional cell carcinoma for another 8%. The rest share the remaining 2% of primary renal malignancies. These tumors present as solid masses or as enhancing elements within cystic lesions, and the treatment is surgical removal. Detailed discussion of the etiologies and pathogenesis of each lesion is beyond the scope of this text. In classifying each tumor, however, pertinent discussion of the clinical presentation, radiologic evaluation, diagnosis, and treatment will be presented.

Renal Cell Carcinoma (RCC)

Accounting for about 90% of all upper urinary tract malignancies and 2 – 3% of all adult malignancies (excluding skin cancer), RCC represents the ninth most common malignancy in white men and the thirteenth most common in women. The majority of patients are diagnosed in the sixth to seventh decades.

Both hereditary and sporadic forms of RCC exist. Familial nonpapillary RCC is associated with a chromosomal translocation that is inherited in an autosomal dominant fashion [35]. RCC is seen in 45% of patients with vHL, an autosomal dominant disease [35]. A third form of familial RCC, known as hereditary familial papillary RCC, has been described [37]. This disease is often bilateral and multifocal, and occurs in younger patients.

The etiology of RCC is unknown, but it appears to be associated with cigarette smoking, and the risk increases proportionately to the duration and number of cigarettes smoked. Additional risk factors for RCC include obesity, especially in women, and diuretic use, which imparts a 3-fold increased risk [40, 41]. Occupational exposure to asbestos may increase the risk of RCC, and leather workers and paperboard printing workers likewise are at increased risk [42 – 44].

Presentation and Diagnosis

RCC can present in a variety of ways. The classic triad of flank pain, hematuria, and a palpable mass is exhibited < 10% of the time, and with current imaging studies, many tu-

mors are being discovered incidentally. Hematuria remains a reliable presenting sign; 60% of patients will display gross or microscopic total painless hematuria. The development of flank pain or presence of a palpable mass suggests the presence of a tumor in an advanced stage. Additionally, the presence of a new variocele, usually on the left, suggests vena cava thrombus. Urine cytology is of little benefit in diagnosing RCC.

RCC may have protean manifestations and paraneoplastic syndromes unrelated to metastases occur in 10 – 40% of patients. Fever occurs in 20% of patients, while hypertension and anemia occurs in 20 – 40% of patients. Secondary erythrocytosis and hypercalcemia occur in 3 – 5% of patients with RCC [46 – 49]. Hepatic dysfunction occurs in 10 – 15% of patients. The alkaline phosphatase is elevated in 15% of patients, as is the prothrombin time and the α2-globulin. This paraneoplastic syndrome, unrelated to metastases, has been named Stauffer's syndrome and portends a poor prognosis [50].

The diagnosis of RCC relies on the algorithm shown in Figure 1. Patients presenting with hematuria, microscopic or gross, with or without constitutional or paraneoplastic syndrome, should undergo excretory urography with nephrotomography. A mass on this study dictates ultrasonography to determine whether it is cystic or solid. Simple cysts by ultrasound criteria terminate the workup (Figure 7a, b). Complex or indeterminant cysts or solid masses require CT, and so it is for RCC. CT has replaced angiography of solid lesions seen on ultrasonography. Rarely, angiography is needed to demonstrate the arterial supply of a tumor. In these cases, the angiogram demonstrates neovascularity, arteriovenous fistulae, and venous pooling in 85 – 90% of the tumors. These tumors likewise enhance with CT contrast infusion. Hypovascular RCCs constitute 10% of tumors and neither displays the above angiographic findings, nor enhances with CT contrast (Figure 8).

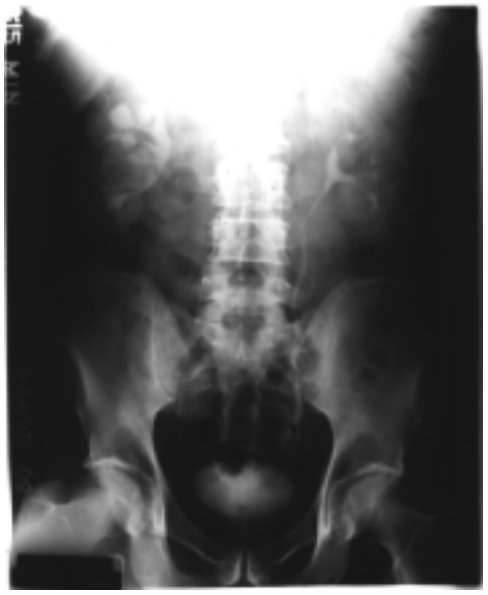

Figure 7a. RCC. White 59 yo white male presenting with gross and microscopic hematuria and right flank discomfort. a) IVP revealed distortion of the calices in the mid portion of the right kidney with a filling defect in the right renal pelvis. Ultrasound showed a solid mass.

The current accuracy of CT is approximately 95% when the typical features of RCC are present [52]. Usually, the mass is isodense or hypodense when compared to the renal parenchyma (15 – 40 Hounsfield units), enhances less than the normal parenchyma with contrast infusion, but may initially appear hyperdense due to its significant vascularity [53]. Invasion of the mass into the surrounding normal parenchyma and central calcification with soft tissue extending beyond the calcification are also highly suggestive of RCC.

When CT cannot be used in patients (e.g. contrast allergy or renal failure) or when CT findings are equivocal, MRI can be used to diagnose RCC with up to 95% accuracy [54].

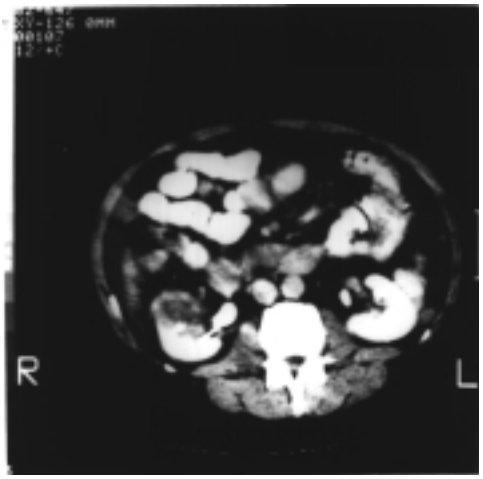

Figure 7b. RCC. White 59 yo white male presenting with gross and microscopic hematuria and right flank discomfort. B) CT confirmed a contrast-enhancing mass in the right kidney without retroperitoneal extension or involvement of the inferior vena cava.

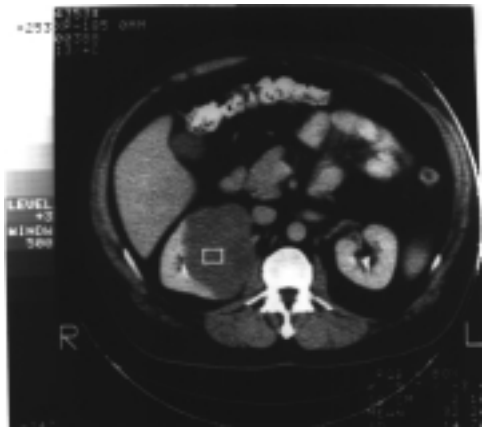

Figure 8. RCC (nonenhancing). A 57 yo white male admitted for evaluation of painless gross hematuria. No other symptoms were reported, and the physical examination was unremarkable. IVP revealed a large 10x12 cm mass in the medial upper pole of the right kidney. Ultrasound revealed an echogenic solid mass. CT revealed a nonenhancing low-density mass measuring 10x12 cm in the upper pole of the right kidney distorting the architecture of the parenchyma and calices. There is no involvement of the inferior vena cava and no adenopathy. In this case, an arteriogram was done confirming a hypovascular to avascular renal mass that distorted the normal renal vasculature. Removal of the mass was indicated.

On T1-weighted images, RCC imparts a signal intensity midway between that of cortex and medulla, and most RCC are hyperintense on T2-weighted images. Currently, MRI serves as a useful adjunct to CT.

Only in rare instances can a diagnosis not be made by imaging techniques. In these cases, FNA can be attempted [53]. If the mass is solid and there is a suspicion of malignancy, then proceeding to surgical exploration or nephrectomy, even without FNA, is warranted.

Renal Urothelial Cancer – Transitional Cell Carcinoma of the Collecting System and Pelvis

Transitional cell carcinoma of the upper tract accounts for about 7% of upper tract tumors, but for only 5% of all transitional cell urothelial tumors. The peak incidence is in the sixth to seventh decade with a 3:1 male-female predominance. Bilateral presentation occurs in 2 – 4% of patients. In patients with Balkan and analgesic abuse nephropathy, the male-female ratio is more equal and the incidence of bilateral presentation is higher.

The etiology of upper tract urothelial cancer is unknown, but several risk factors have been identified. Cigarette smoking, caffeine ingestion, exposure to chemicals used in the tile and rubber industries, chronic urinary infection, analgesic abuse, and Balkan nephropathy have been implicated in urothelial cancer [56, 57].

Patients present with microscopic or gross hematuria 75 – 95% of the time and with total hematuria on the 3 glass test, not unlike RCC

[58]. Flank pain may occur in 30 – 40% of patients, but a palpable flank mass occurs only in < 15% of patients. Constitutional symptoms (fever, anorexia) are late events in 7 – 10% of patients and suggest disseminated disease.

Evaluation often begins with excretory urography workup for hematuria. An abnormal filling defect intrinsic to the collecting system is present in 50 – 75% of studies where urothelial cancer is involved. Complete obstruction of the renal pelvis resulting in nonvisualization occurs in 10% of the urograms. Other causes of filling defects include nonopaque renal calculi, blood clots, sloughed papilla, fungus balls, or a hemangioma. Ultrasonography is helpful in differentiating a stone from a tumor but has no further value.

CT is a useful diagnostic test in urothelial tumor and is used to delineate pelvic filling defects when the mass is large (Figure 9a). In comparison to normal parenchyma, urothelial tumors appear hypodense upon contrast administration. This also aids in differentiation from RCC [59, 60]. MRI is of undetermined value in the evaluation of urothelial tumors. Angiography may differentiate RCC from urothelial carcinoma (the latter will not have the hypervascularity of the former) but is more invasive and expensive than CT (Figure 9b). The treatment of choice is nephroureterectomy, because a urothelial tumor must be considered a tumor of the entire urothelium.

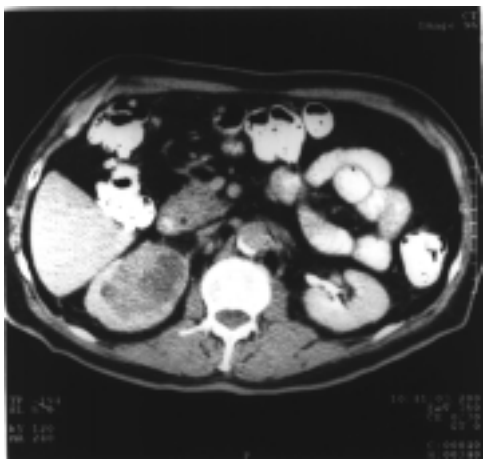

Figure 9a. Urothelial cancer (transitional cell). A 78 yo white male with painless gross hematuria, no history of trauma, and an unremarkable physical examination. a) CT of the abdomen shows right-sided hydronephrosis with high attenuation in the collecting system, probably representing hemorrhage. From this study, a mass could not be excluded.

Other Primary Malignant Tumors

Primary renal sarcomas and adult Wilms tumor account for only 2 – 3% of primary renal malignancies. There are no significant distinguishing features to differentiate them from RCC, and surgical removal is always indicated. Sarcomas are thought to arise from the renal capsule or renal vasculature. Leiomyosarcoma is the most common, constituting 60% of renal sarcomas with liposarcomas accounting for another 20% [61, 62]. Malignant fibrous histiocytomas (fibrosarcomas) rarely arise in the kidney and cannot be preoperatively differentiated from RCC. Finally, hemangiopericytoma, originating from pericytes which envelope capillaries and aid in blood flow, accounts for 20 reported cases [63].

Renal sarcomas often grow to be quite large and present with symptoms not unlike other renal tumors, including flank pain or abdominal pain, hematuria, and a palpable mass. Radical nephrectomy is indicated in all sarcomas and the prognosis is generally poor, especially for malignant fibrous histiocytoma [61].

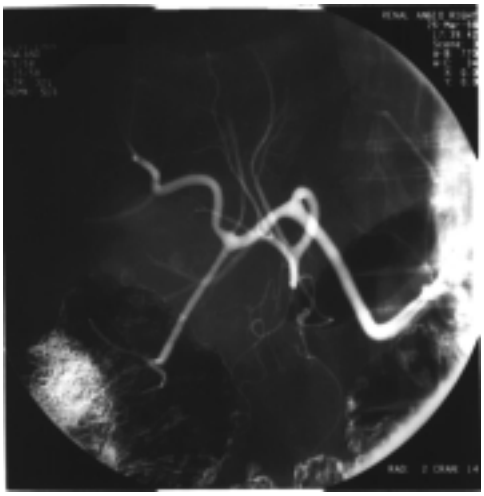

Figure 9b. Urothelial cancer (transitional cell). A 78 yo white male with painless gross hematuria, no history of trauma, and an unremarkable physical examination. b) A right renal arteriogram was performed showing fine neovascularity in the region of the right uretero pelvic junction with splaying of the segmental renal arterial branches. There are no underlying arteriovenous malformations as with renal cell carcinoma.

Primary Retroperitoneal Tumors

Benign retroperitoneal tumors account for only about 20% of retroperitoneal masses. For the most part, they are the benign counterparts of more malignant processes and include lipomas and leiomyomas. The majority of retroperitoneal masses are malignant with 80 – 90% being lymphomas and sarcomas. The most common sarcoma arising from the retroperitoneum is liposarcoma followed by fibrosarcoma and leiomyosarcoma [64]. As with sarcomas of the kidney, retroperitoneal sarcomas do not produce symptoms until they are large, at which time abdominal pain and a palpable mass may be evident. The patient may have the constitutional symptoms of fever, weight loss, and malaise. CT is the most valuable imaging study, and radical resection with wide margins is the treatment of choice for sarcomas, whereas lymphomas are best treated with chemotherapy and/or radiotherapy.

Renal Masses Due to Infection: Xanthogranulomatous Pyelonephritis and Malakoplakia

Xanthogranulomatous pyelonephritis is a specific presentation of chronic recurrent bacterial pyelonephritis. It occurs mostly in the elderly, with 70% of the 300 cases reported occurring in women [66]. Its presentation may be similar to malignant renal tumors, in that there may be recurrent flank pain, constitutional symptoms such as fever, weight loss, malaise, fatigue, hematuria, and anemia. Hepatic enzyme elevation occurs in 15 – 25% of patients [67]. Pyuria exists in 75% of patients, and urine cultures are positive for *Proteus mirabilis* in 66% of patients, *E. coli* and *Klebsiella sp* in 33% of patients, and *Staphylococcus aureus* in the remaining few. Multiple pathogens can be present in about one-fourth of the patients, albeit some patients present with culture-negative urine despite ongoing disease activity [67, 68]. Patients have a history of recurrent urinary tract infections (UTI) often complicated by struvite calculi and/or obstruction. Intravenous urography may show a mass with calcific densities present. The mass may be cavitary, have a cystic appearance, and must be differentiated from a malignant tumor. Notably, urography may reveal a nonfunctioning kidney in 80% of patients [67]. Sonography reveals a solid or sometimes cystic structure with distorted architecture, with or without obstruction, frequent echogenic shadows characteristic of stones, and echogenic amorphous material with some attenuation of sound distally. CT reveals an enlarged kidney with distorted architecture, low density due to the fat content,

the presence of stones, and poor to absent enhancement. Differentiation cannot be made from RCC, and MRI is of little added value. The treatment should be surgical removal, at which time a pathologic diagnosis can be made. Fortunately, the disease rarely involves both kidneys.

Malakoplakia is a rare granulomatous disease of uncertain etiology that occurs in the same clinical setting as Xanthogranulomatous pyelonephritis. Over 200 cases have been reported. Unlike patients with xanthogranulomatous pyelonephritis, patients with malakoplakia usually have positive cultures for E. coli rather than Proteus mirabilis, and the disease is bilateral in 50% of patients [69]. Fever and flank pain are present in upper tract malakoplakia, and a palpable mass may be present [70]. Excretory urography reveals enlarged kidneys with distorted architecture and multiple filling defects. CT is relatively unhelpful in rendering a specific diagnosis, and exploration or removal of the lesion imparts both diagnosis and treatment.

Summary

In conclusion, greater than 90% of renal masses can be diagnosed by radiographic techniques using the algorithm developed over the last 25 years and discussed in this chapter. FNA biopsy is rarely needed, but may be used if the diagnosis is unclear and a renal sparing operation rather than radical nephrectomy is being considered. Simple cysts (Bosniak class I) can be reliably diagnosed by ultrasonic and CT imaging and should be left alone. More complicated class II lesions and some class III lesions should be followed, or in the latter case explored or removed, because almost 50% are malignant. Patients with cysts with contrast-enhancing elements (class IV) and solid tumors should undergo an operative procedure, unless the mass is a lymphoma or can be proven to be benign radiographically, as is the case with a renal hamartoma (angiomyolipoma).

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Acute Renal Failure

Sean Leavey and David Humes

Introduction

Acute renal failure (ARF) is a common clinical syndrome characterized by an abrupt deterioration in kidney function resulting in abnormalities in volume-regulatory, metabolic-regulatory, excretory, and endocrine functions. At presentation, ARF is roughly evenly divided between patients who are oliguric (produce < 400 mL/day urine output) and those who are nonoliguric (produce > 400 mL/day urine output). Most clinicians would accept a rise in the serum creatinine concentration of > 0.5 mg/dL/day and a rise in the blood urea nitrogen (BUN) level of > 10 mg/dL/day over several days as diagnostic of ARF. Many definitions can and have been proposed for ARF. In one review of 28 different studies, no two used the same diagnostic criteria [47]. It is not clear, in fact, whether an optimal definition exists. The syndrome of ARF has multiple causes, diverse manifestations, and a clinical presentation covering a continuum from mild to life-threatening disease. A patient may progress from normal renal function to dialysis-dependent ARF within a few days.

ARF may evolve from diminished renal blood flow (RBF), termed prerenal functional ARF; from an acute severe parenchymal insult, termed intranenal structural ARF; or from obstruction to urine flow termed postrenal obstructive ARF. Intrarenal ARF is further characterized according to the site of injury as a primarily vascular, glomerular, tubular, or interstitial process. The relative contributions of different etiologies to the development of ARF vary between community-based and hospital-based populations; and within the hospital, between medical intensive care unit, surgical intensive care unit, and nonintensive care unit populations. Prerenal azotemia, for instance, accounts for some 70% of community-acquired and 40% of hospital-acquired ARF. Intrarenal causes account for at least 50% of hospital-acquired ARF but are less common in community-acquired cases.

ARF is present on admission to hospital in 1% of cases and further complicates up to 5% of admissions. The mean age of affected individuals has increased such that 36% of patients in one recent hospital survey were > 70 years old at presentation [37]. Despite decades of improvements in the provision of intensive care and specifically in the provision of renal replacement therapy, the morbidity and mortality associated with ARF remains extremely high. The percentage of patients with ARF requiring dialytic intervention ranges from 20 – 60%. Of those requiring dialysis who survive, 12 – 33% have been reported to require long-term renal replacement. The mortality in dialysis-requiring ARF is generally reported to be ≥ 50%, while the mortality in those admitted to the hospital with prerenal azotemia is approximately 7%. For example, a recent cohort analytic study reported mortality rates of 62%, 31%, and 7% in matched groups who developed dialysis-requiring, nondialysis-requiring, or no ARF, following a contrast procedure [36]. A mortality rate of 63.7% was noted in those with

dialysis-requiring ARF vs. 4.3% in those without ARF in a prospective cohort study of 43,642 patients after open cardiac surgery [7].

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) reported a median duration of survival for a group of 490 seriously ill patients with dialysis-requiring ARF of only 32 days [28]. Only 27% of patients in this report were alive after 6 months, but of those who survived 62% rated their quality of life as good. The overall estimated cost (in 1994 US dollars) per quality-adjusted life year saved by initiating dialysis and continuing aggressive care in this group of patients was $128,200. When the patients were stratified into prognostic categories, the estimated cost per quality-adjusted life year saved was $274,100 vs. $61,900 for those in the worst and best prognostic categories, respectively.

ARF is a serious, common, complicated, and costly medical illness.

Approach to the Differential Diagnosis of ARF

General Comments

There is often more than one contributing etiologic factor in an ARF presentation, and a broad consideration of all possible causes is necessary. The time-honored approach to establishing a diagnosis in renal disease rests on 1) localizing the predominant site(s) of renal injury and 2) establishing the temporal course of the event(s) leading to the presentation. If the process is localized to prerenal or postrenal sites, the treatment required is restoration of normal perfusion or relief of obstruction, and, notwithstanding the recognition that there are many causes of pre- and postrenal ARF, the specific diagnosis is often easily made. In intrarenal ARF (be it primarily due to vascular, glomerular, tubular, or interstitial processes), specific treatments are less readily available and recovery of renal function in those who survive is slower and less certain.

An elevation in BUN and creatinine may be acute, acute on chronic, or chronic. In a patient with recently measured and available BUN and creatinine levels, determining which is the case may be easy, e.g. a patient who develops ARF as an iatrogenic complication during a hospital admission. However, the distinction must be made in all cases because a delay in the diagnosis and treatment of acute (or acute on chronic) renal failure may allow a prerenal syndrome to progress to established acute tubular necrosis (ATN), a potentially treatable intrinsic renal process such as renal vasculitis to progress to ESRD, or a potentially life-threatening metabolic complication to develop in any patient with deteriorating renal function. Features that suggest chronicity are summarized in Table 1. Most of these are nonspecific. If doubt exists as to the nature of the temporal onset of the renal failure, then it should be treated as acute until proven otherwise.

Prerenal Functional Azotemia

Prerenal azotemia results from a persistent, significant decline in renal blood flow (RBF) that overcomes autoregulatory mechanisms producing a reduction in glomerular filtration rate (GFR) and hence a rise in BUN and serum creatinine concentrations. Implicit in the functional component of the definition is that complete reversibility of prerenal ARF occurs with restoration of RBF. Often more than one

Table 1. Factors Suggestive of Chronicity*

History
- Prior diagnosis of renal impairment
- Remote / Prolonged history of proteinuria or hematuria
- Family history of hereditary renal disease (i.e. ADPKD)
- Long history of systemic illness
- Long duration/evolution of presenting symptoms

Physical Examination
- Ballotable polycystic kidneys

Urinalysis
- Broad casts

Laboratory Tests
- Anemia of chronic disease
- Percent carbamylated hemoglobin

Radiology
- Small kidneys

*Unless there is clear historical evidence indicating chronic renal failure or bilateral small scarred kidneys renal failure should be treated as acute until proven otherwise.

etiologic factor will be present. The causes of prerenal azotemia are listed in Table 2. Medications that interfere with autoregulatory mechanisms in the kidney are included in the list. A nonlinear relationship exists between serum creatinine concentration and GFR. As a result, individuals with chronic renal insufficiency exposed to prerenal insults are susceptible to more dramatic increases in BUN and serum creatinine concentrations. In chronic renal failure, prerenal effects are common and should be considered before activity or progression of the primary renal disease is invoked to explain a rise in BUN and creatinine.

A careful history for gastrointestinal, skin, and renal salt and water losses, or for bleeding is important. The symptoms of thirst or orthostatic dizziness may be important diagnostic clues. A complete history of drug ingestion, including prescription and nonprescription medications, is often instructive. Symptoms indicating other underlying etiologies may be apparent in the presenting complaint and should be sought in a thorough systems review. Physical exam needs to be complete. The history may direct a search for signs of chronic liver disease, congestive heart failure (CHF) or other specific etiologies. An assessment of intravascular volume status is always necessary. This should include a search for orthostatic hypotension and tachycardia and assessment of jugular venous pressure, skin turgor, and moistness of mucous membranes. (Table 3).

Jugular venous pressure can be measured with the patient reclined at any angle, as the vertical distance separating two imaginary horizontal lines that correspond respectively to the level of the manubriosternal angle and top of the neck vein pulsation (assuming the top of the venous pulsation in the neck is visible). In the envolemic state, when the head of a patient's bed is elevated to a 45° angle, neck vein pulsation is just visible at the root of the neck. Likewise, in this position an external jugular vein allowed to fill from above by occlusive external compression at the root of the neck will empty briskly with release of occlusive pressure. However, when intravascular volume is low, even with the patient lying perfectly flat, neck vein pulsation may be absent, and an external jugular vein allowed to fill from above by external compression will continue to empty briskly when the compression is removed.

Postrenal Obstructive ARF (Chapter I-14)

Common causes of ARF from obstruction include benign prostatic hypertrophy or prostatic carcinoma in men leading to obstruction of the bladder outlet; carcinoma of the uterine cervix in women leading to either obstruction

Table 2. Etiology of Acute Renal Failure

ARF → Anuric:
- Bilateral renovascular occlusion
- Severe acute glomerulonephritis
- Acute cortical necrosis
- Bilateral ureteric obstruction
- Bladder outflow obstruction

↓ *Oliguric/Non Oliguric:

Prerenal "functional" ARF	*Intrarenal "structural" ARF*	*Postrenal "obstructive" ARF*
Hypotension	*Tubular*	*Intrarenal*
Volume Depletion	Ischemic ATN	Acute uric acid nephropathy
Extrarenal sodium loss	Any of the causes of prerenal ARF	Etylene glycol poisoning
Gastrointestinal losses	Nephrotoxic ATN	Drugs (methotrexate, acyclovir, sulfonamides, gallium nitrate)
Vomiting, Diarrhea,	Antibiotics (aminoglycosides, amphotericin B...)	*Extrarenal (chapter I-14)*
Fistulae, Bleeding	Heavy metals (cisplatin)	
Skin losses	Anti-cancer drugs (ifosfamide)	
Burns, Heat exposure	Immunosuppressives (cyclosporine, FK506)	
Intrarenal sodium loss	Radiocontrast agents	
Mineralocorticoid deficiency	Endogenous toxins (myoglobin, light chains, hemoglobin)	
Diuretic exposure	*Acute tubulointerstitial nephritis*	
Osmotic diuresis (hyperglycemia, uremia, mannitol)	*Vascular*	
Salt-wasting nephropathy	Atheroembolic disease	
Third-Space fluid sequestration	Small vessel vasculitis	
Cirrhosis,CHF,	Malignant hypertension	
Nephrotic syndrome	Scleroderma renal crisis	
Pancreatitis, Crush injury,	Thrombotic microangiopathies	
Other ...	*Acute glomerulonephritis*	
Hepatorenal syndrome		
Drug-related		
Nonsteroidal antlinflammatory drugs		
ACE inhibitors		
Amphotericin B		
Cyclosporine / FK506		
Interleukin 2		

*Always consider possibility of multiple coexisting etiologies

of the bladder outlet or ureter bilaterally; and a blocked Foley catheter in hospitalized patients. Other pelvic or retroperitoneal tumors may also cause obstruction. A blood clot, stone, or tumor within the lumen of the lower urinary tract in the bladder, ureter bilaterally, or single ureter in the case of a transplanted or a solitary native kidney, can produce a similar result. Neurogenic bladder is also a common finding, especially in diabetic patients. Drugs with anticholinergic side effects or the postoperative state may precipitate urinary retention in predisposed individuals. Intrarenal obstruction due to precipitation of crystals within the tubules is rare. It is considered here in the differential diagnosis, although this

Table 3. An Approach to the Differential Diagnosis of ARF

ARF Evaluation
↓

Steps: 1-2 History and Physical Exam ↓	→	3 List Plausible Contributing Factors	→	4-5 Urinalysis and Diagnostic Indices (interpret in context of 1-3)	→	6 Decide on Probable Cause(s) (consider coexisting etiologies)	→	7 Confirmatory Tests (as/if needed)

	Prerenal ARF	*Intrarenal ARF*	*Postrenal ARF*
1. History	Thirst Orthostatic Symptoms Weight loss Vomiting, Diarrhea, Hematemesis,Melena Diuretic use, Polyuria Exposure to certain drugs Disease specific symptoms for CHF, Cirrhosis	Likely Ischemic ATN Hypotension or shock Prolonged/severe prerenal symptoms Nephrotoxic Exposure Radiocontrast, Recent medications, Bone pain Likely pigment exposure: Excessive exercise, Seizures, Excess alcohol ingestion, Physical injury Tubulointerstial /Vascular/ Glomerular Rash, Arthralgias, Fever Angiography, Vascular surgery Strep infection, Hemoptysis, Intravenous drug abuse	Extrarenal Frequency, Nocturia, Hesitancy, Poor stream, Post-void dribbling, Double micturition, Incontinence Hematuria, Colic, Suprapubic/ flank pain Diabetic neuropathy,Anti-cholinergic drug exposure Postoperative patient Intrarenal Drug exposure Intoxication
2. Physical Examination	Orthostatic tachycardia and hypotension Decreased jugular venous pressure, Reduced skin turgor, Dry mucous membranes Disease specific signs: e.g. Displaced apex, Gallup rhythm, Rales, Parasternal heave, JVD, Hepatomegaly, Ascites, Edema in CHF; ...	Signs of prerenal disease Muscle tenderness Maculopapular rash Palpable purpuric rash, Livedo reticularis Digital infarcts, Retinal “cholesterol” embolus New murmur, Extracardiac signs of endocarditis	Bladder distension by palpation or percussion Enlarged prostate Palpable pelvic mass on internal examination
3. List Plausible Diagnoses (Table 2)	Prerenal Causes ...	Intrarenal Causes...	Postrenal Causes...

Table 3. Continuation

	Prerenal ARF	*Intrarenal ARF*		*Postrenal ARF*	
4. Urinalysis	Typical ‘‘bland" S.G. > 1.018, Neg/Tr Protein Neg heme Cells: none Casts: hyaline Atypical “Active” Additional/ other etiology likely	Typical “active” S.G. 1.010, 1+ to 3+ Protein Heme + or - Cells & Casts: RBC, WBC, Tubular epithelial cells free or in casts, granular casts	Atypical “bland” Other etiology likely	Typical S.G. > 1.010, Neg/1+Protein Heme – or + Cells & Casts: None or RBCs or WBCs, possible but tubular epithelial in cells and cellular or granular casts not expected	Atypical proteinuria or non- hyaline casts suggest intrarenal cause
5. Diagnostic Indices	Typical (any cause) FE_{Na} < 1% Urine sodium < 20 mM But Fe_{Na} > 1% or Urine sodium > 20 mEq/1 Can be seen with diuretic use, preexisting chronic renal failure, salt wasting nephropathy, and/or a non prerenal etiology	Typical (any cause of ATN) FENa < 1% Urine sodium > 20 mEqA But FeNa < 1% or Urine sodium < 20 mM Can be seen with Radiocontrast exposure Pigment exposure Advanced liver disease Early measurement in Interstitial nephritis Acute GN Coexisting prerenal state		Generally not useful in the diagnosis of postrenal ARF	
6. Decide on probable cause / causes & 7. Order confirmatory tests as indicated					

syndrome is not truly postrenal. Causes of intrarenal obstruction include acute uric acid nephropathy, ethylene glycol toxicity complicated by calcium oxalate precipitation, and drugs such as methotrexate, acyclovir, and sulfonamides.

A detailed history, including a drug history, may suggest obstructive ARF. Complete anuria in ARF is rare and generally narrows the differential diagnosis to an obstructive etiology, renovascular occlusive etiology, severe acute glomerulonephritis, or a catastrophic ischemic event such as acute major bleeding – as described in obstetric cases of acute cortical necrosis (Table 2). However, the urine output is a poor indicator of underlying obstructive problems because polyuria, alternating oliguria and polyuria, anuria, or an

apparently normal urine output may all be seen. Specific symptom complexes may point to prostatic disease, bladder outlet obstruction, or stone disease. The physical exam should assess for a distended bladder, a pelvic mass, and an enlarged prostate. When bladder distension is suspected, measurement of a postvoid residual volume by straight catheterization is diagnostically helpful.

Intrarenal Structural ARF

The causes of intrarenal ARF (Table 2) are grouped into categories based on localization of the dominant injury. Tubular pathology defining the clinical syndrome of ATN accounts for the majority of the cases of intrarenal ARF. ATN is the result of either ischemic or nephrotoxic tubular injury. Ischemic ATN and prerenal azotemia are at opposite poles of a continuum of renal injury resulting from hypoperfusion. A prerenal azotemic state left untreated may progress towards established ATN. Toxic and drug-related causes of ATN are listed separately (Table 6). Acute tubulointerstitial nephritis may account for approximately 10% of cases of intrarenal ARF, and may be idiopathic or more often secondary to drugs, toxins, autoimmune, idiopathic, or infective processes. Among the vascular causes, atheroembolic disease is suggested to be underrecognized as a factor in ARF presentations [41]. It may occur spontaneously or as a complication of cardiac catheterization, vascular, and cardiac surgical procedures (Part I, Chapter 6). Glomerular diseases account for about 5% of intrarenal ARF and include, in addition to vasculitic syndromes, all other causes of rapidly progressive glomerulonephritis (RPGN).

A history of systemic disease, fever, chills, IV drug use, arthralgia, skin rash, recent infection, sinusitis, hemoptysis, hematuria, or recent drug exposure may point towards glomerular or interstitial pathologies. Recent exposure to exogenous toxins or a history of immobilization, seizure, skeletal muscle injury, or ethanol intoxication may point towards a nephrotoxic etiology. Clues from the physical examination may include acrocyanosis, digital infarction, livedo reticulosis or funduscopic evidence of cholesterol emboli in atheroembolic disease; skin rash or palpable purpura in vasculitis; petechia and nonpalpable purpura in hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP); sclerodactylia in systemic sclerosis; a new murmur, fever, splinter hemorrhages, Osler's nodes, Janeway lesions, or Roth spots in infective endocarditis; a maculopapular erythematous rash in allergic interstitial nephritis; and muscle tenderness in rhabdomyolysis.

Urinalysis and Diagnostic Indices in the Differential Diagnosis of ARF

Urinalysis should be performed in all cases and should include, at the very least, reagent strip testing and microscopy of a freshly-spun sediment. Measurement of urinary biochemical indices may provide additional information. Urinalysis data are interpreted in the context of the clinical situation in which they are obtained. Specifically, the urinalysis is used to aid localization of and differentiation between likely causes of ARF (Table 3). In essence, one interrogates the ability of the glomeruli and tubules to elaborate urine appropriately. From this, one attempts to derive an indication of nephron structural and functional integrity.

Red cells, not normally present in the urine, can enter the urinary tract anywhere from the glomerulus to the tip of the urethra. In prerenal disease, they are unexpected unless sec-

ondary to traumatic catheterization. In postrenal disease, they may reflect underlying pathology in the lower urinary tract. If present in the form of casts, however, they are indicative of intrarenal disease and almost always a glomerulopathy. The presence of detectable heme pigment in the absence of microscopic hematuria points towards a rhabdomyolytic or hemoglobinuric pigment-induced ARF.

White cells also may arise from anywhere along the urinary tract, from the glomerulus to the tip of the urethra. The common thought to consider them only indicative of a lower UTI (a common etiology of leukocyturia) needs to be guarded against in ARF patients. Intrarenal inflammation or infection also need to be considered. Again, the presence of white cell casts or white cells in the company of granular casts or significant proteinuria heralds an intrarenal cause. Possibilities include interstitial nephritis, acute glomerulonephritis, and pyelonephritis.

Tubular epithelial cells (present < 1 per several high-powered fields in normal urine) are frequently seen in intrarenal ARF. Intact cells may be seen free or within tubular epithelial cell casts or degraded as constituents of the granular casts. Muddy-brown granular casts are particularly classical for acute tubular necrosis.

Large quantities of protein are indicative of intrarenal disease, while trace to 1+ proteinuria may be present in the concentrated urine of prerenal azotemia or sometimes in postrenal azotemia. Quantitatively, in an adult > 2g of proteinuria in 24 hours, or a urine protein to creatinine ratio > 2, is suggestive of underlying glomerular disease (nephrotic range proteinuria > 3.5g/1.72m^2/day is pathognomonic of glomerular disease). Tubular disease typically is associated with < 2g (urine protein to creatinine ratio < 2) per 24 hours of proteinuria. Qualitatively, glomerular and tubular proteinuria are distinguished based on size and charge characteristics by urine protein electrophoresis. Leakage of larger molecular weight proteins is associated with glomerular disease. The predominantly positively-charged immunoglobulin light chains responsible for nephrotoxic ATN in multiple myeloma are characteristically missed by reagent tests, which preferentially detect anionic (negatively-charged) proteins. Gram quantities of Bence-Jones proteinuria may be present with a negative urine dipstick for protein and must always be sought for directly in adult patients with unexplained renal failure.

Diagnostic indices reflecting the tubular capacity to handle solutes and water help differentiate prerenal azotemia from ischemic ATN. The context in which the measurements are taken determines the expected results. In general, if a state of absolute or relative decreased effective arterial volume is present, then, in the absence of pharmacologic inhibition, healthy kidney tubules should maximally reabsorb solutes and water. Whereas in prerenal azotemia this should be possible, in ATN maximal reabsorptive capacities are reduced. Diagnostic indices provide corroborative evidence for suspected diagnoses. It should be recognized, however, that they may be misleading, if interpreted in isolation, without regard for the entire clinical context.

The reabsorption of water is dependent on tubular integrity, antidiuretic hormone (ADH), and the maintenance of the medullary hypertonicity concentration gradient. In respect of ADH secretion, protection of volume will take precedence over protection of osmolality. A concentrated urine with an increased urine osmolality and an increased urine creatinine to plasma creatinine ratio is expected in prerenal disease vs. ATN. As shown in Figure 1, the absolute discriminating value of these 2 indices of water reabsorption with respect to prerenal azotemia in ATN is poor, with considerable overlap.

Overlap between diagnostic indices in prerenal azotemia and ATN exists when solute reabsorption in the form of urea nitrogen is considered. As opposed to creatinine, urea nitrogen is significantly reabsorbed by healthy tubules, and more avidly so when the kidney is underperfused. The BUN to serum creatinine ratio describes this difference. Attempts to separate prerenal disease and ATN based on this ratio have suggested that a BUN to serum creatinine ratio > 20:1 is indicative of prerenal disease. However, BUN concentrations and creatinine concentrations are both subject to many influences independent of the state of renal perfusion and tubular integrity.

Urine sodium concentration is also frequently measured in an effort to differentiate between prerenal azotemia and ischemic ATN. A urine sodium < 20 mM is suggestive of prerenal disease, while one > 40 mM is suggestive of ATN. Overlap persists between these 2 syndromes in terms of urine sodium concentration, and additional factors can impact urine sodium concentrations (Table 3). Perhaps the most frequently used diagnostic index is the fractional excretion of sodium (FE_{Na}). It is derived from the urine-to-plasma sodium ratio divided by the urine-to-plasma creatinine ratio, multiplied by 100, and is expressed as a percentage (Figure 1). It is therefore an integrated index describing the extraction of sodium and water from the glomerular filtrate. FE_{NA} is the most sensitive index to differentiate pre- vs. intrarenal disease: an FE_{Na} < 1% suggests prerenal disease, while an FE_{Na} > 1% suggests ATN. However, nonazotemic patients in sodium balance will often have an FE_{Na} of < 1%, because the amount of sodium reabsorbed to maintain homeostasis (in those on a normal salt diet) is typically > 99% of the sodium filtered. Similarly, an FE_{Na} of < 1% in ARF has been described in intrarenal and postrenal disease and an elevated FE_{Na} is occasionally seen with prerenal disease [61] (Table 3).

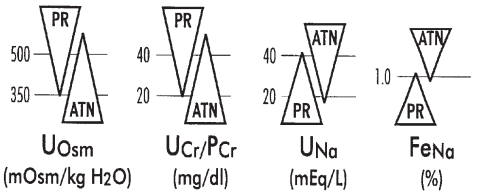

Figure 1. Diagnostic indices in acute renal failure. The horizontal axis displays four laboratory tests and the units used to differentiate functional prerenal (PR) azotemia from acute tubular necrosis (ATN). The vertical axis depicts values that define the nondiagnostic zones of overlap between the designated values and diagnostic areas of nonoverlap above and below the designated values. The derived urinary index, the fractional excretion of sodium (FE_{Na}), has essentially no nondiagnostic overlap zone (exceptions discussed in text). The fraction of the filtered sodium FE_{Na} can be calculated from a urine specimen:

$$FE_{Na}(\%) = \frac{\text{quantity of sodium excreted}}{\text{quantity of sodium filtered}} \times 100$$

Because the quantity of sodium excreted is equal to the product of the urine sodium concentration (U_{Na}) and the urine volume (V); the quantity of sodium filtered is equal to the product of the plasma sodium concentration (P_{Na}) and the GFR (or creatinine clearance, $C_{Cr} = U_{Cr} \times V/P_{Cr}$):

$$FE_{Na}(\%) = \frac{U_{Na} \times V}{P_{Na} \times (U_{Cr} V / P_{Cr})} \times 100 = \frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$$

[Kelley WN (ed) 1997 Internal Medicine. Lippincott-Raven, Philadelphia, 934]

Confirmatory Tests in the Differential Diagnosis of ARF

Specific additional tests useful in the differential diagnosis of ARF are shown in Table 4. Among these, renal ultrasound is often used to evaluate for a postrenal cause of ARF. It is usually diagnostic in this setting, although bilateral pelvicaliectasis may not have had time to develop in acute obstruction, and in rare conditions the lower urinary tract is encased and nondistensible, as can occur in retroperitoneal fibrosis. Ultrasound also confirms the presence of two kidneys and pro-

Table 4. Specific / Confirmatory Tests in the Approach to the Differential Diagnosis of ARF

Prerenal ARF
Response to restoration of intravascular volume
or reduction/cessation of drug-related factor
Investigation of underlying disease state
e.g. liver evaluation, cardiac evaluation,
ACTH stimulation fest
Intrarenal ARF
Ischemic ATN: Workup of unexplained hypotension as indicated
Drug-related ATN: Monitoring serum drug levels
Multiple myeloma: serum protein electrophoresis and urine immunoelectrophoresis, skeletal survey, bone marrow aspirate, +/- kidney biopsy
Rhabdomyolysis: CK and aldolase concentrations
Hemolysis: haptoglobin, free serum and urine hemoglobin estimation, LDH level, direct antiglobulin test
Acute tubulointerstitial nephritis: Serum and urine eosinophils, kidney biopsy
Atheroembolic Disease: LDH, C3/CH50 complement, absolute eosinophil count
Thrombotic microangiopathy: stool cultures for VTEC, LDH, platelet count, reticulcyte count, haptoglobin
Vasculitis and/or glomerulonephritis: quantitation of urinary protein excretion, ANCA, ANA, anti-GBM antibody, C3, C4 and total complements, ASO titer, hepatitic serologies, kidney biopsy
Postrenal ARF
Renal ultrasound
Other noninvasive / invasive procedures as required
Measurement of post-void residual volume

ACTH: adrenocorticotropic hormone, ANCA: antineutrophil cytoplasmic autoantibody, ANA: antinuclear antibody, CK: creatine kinase, LDH: lactate dehydrogenase, VTEC: verotoxigenic E. coli, GBM: glomerular basement, ASO: antistreptolysin O

vides a measure of renal size, useful in the distinction between chronic and acute disease (Table 1). Doppler ultrasound provides information regarding perfusion and resistive indices. The resistive index is derived from dividing the peak systolic excursion on Doppler waveform analysis by the peak systolic minus the peak diastolic excursion. In a nonspecific manner, the resistive index approaches unity with various pathological conditions that perturb diastolic arterial flow to a greater extent than systolic arterial flow. In general, interstitial swelling or obstruction may produce such an effect. In studies of normal kidneys, the probability that a single measurement of the resistive index is > 0.7 was estimated to be 6%, while the probability that an average of 3 readings is > 0.7 was estimated to be 3% [32]. Therefore, a resistive index > 0.7 should raise suspicions for an underlying abnormality.

Summary

Table 3 details a stepwise approach to the evaluation of ARF. ARF is a complex disorder and several contributing factors may play a role in the same case. A careful history and physical examination will generate a list of plausible causes, and is complemented by a skillful interpretation of urinalysis and appropriate laboratory and radiologic investiga-

tions. This approach will lead to the correct diagnoses in most cases. If the case does not fit comfortably into the categories of prerenal and postrenal disease or ATN, then resolution of the diagnostic dilemma will generally require a renal biopsy. Failure to do this could lead to missing treatable diseases [51].

Pathophysiological Mechanisms in ARF

This section deals specifically with pathologic mechanisms that relate to the development of ischemic or nephrotoxic ATN. Significant progress has been made in unraveling the multiple, synergistic, and interdependent mechanisms involved in generating ATN. The term ATN is somewhat a misnomer because renal failure in this syndrome produces typically only patchy segmental necrosis in the tubules, *but* it appropriately directs attention on tubular injury as the focal point for understanding the pathogenesis. The clinical course of ATN can be considered in terms of 3 phases: an initiation phase, a maintenance phase (where the triggering factors of ARF have ceased to exist, but the renal failure continues), and a recovery phase. In the clinical setting, these phases may overlap, although ongoing triggering events may hamper ongoing recovery. These events will be discussed separately.

Initiation Phase – Hemodynamic Alterations [45]

Any cause of a significant decline in absolute or relative effective arterial blood volume results in a decrease in perfusion of vital organs and a fall in mean arterial pressure. Both central and peripheral baroreceptors are activated to initiate neurohumoral compensatory mechanisms, including an increase in cardiac contractility and venous and arteriolar vasoconstriction, to improve the perfusion of vital organs and maintain blood pressure. A variety of vasoactive substances are released locally and systematically to promote arteriolar contraction, primarily in the renal, splanchnic, and musculocutaneous circulatory beds. In the kidney alterations in levels of angiotensin II (Ang II), endothelin, sympathetic amines and endothelial-derived relaxant factor are important. Initially, in response to a global reduction in RBF, preferential vasoconstriction of efferent postglomerular arterioles attempts to maintain glomerular perfusion pressure and GFR. Sustained significant reductions in RBF override this mechanism, however, and result in substantial declines in GFR. Contraction of glomerular mesangial cells in response to mediators of vasoconstriction may also contribute to the decrease in GFR by reducing the surface area for filtration.

Initiation Phase – Medullary Hypoxemia [4]

Normal renal physiology requires generation and maintenance of a medullary hypertonicity gradient. It is achieved via a countercurrent system of blood vessels and tubules in the renal medulla. As a direct consequence of countercurrent transport, oxygen levels in the medullary interstitium are decidedly low. Active transport processes in the straight segment of the proximal tubule (S3) and in the medullary thick ascending limb of the loop of Henle therefore take place in a zone of relative regional hypoperfusion and relative hypoxia – the outer medulla. The ATP-dependent ac-

tive transport processes dictate the demand for, while perfusion and blood oxygen content dictate the supply of, oxygen in a delicately balanced system. As RBF decreases, medullary hypoxemia can rapidly ensue. A variety of agents attempt to regulate oxygen homeostasis in these circumstances, including vasodilatory prostaglandins, nitric oxide, dopamine, and adenosine. A redistribution of blood flow may help, both by reducing GFR and therefore tubular workload, and by increasing oxygen delivery to the tubules. Some mediators may also directly inhibit transport processes and in this way further reduce tubular workload. However, as adaptive responses are overwhelmed, tubular injury inevitably ensues.

Initiation Phase – Tubular Injury

Nephrotoxic or ischemic insults can cause tubular injury. Insults may occur separately or in various combinations, e.g. the shocked patient on aminoglycoside antibiotics or the dehydrated patient with myeloma who receives an injection of radiocontrast. Nephrons are typically injured focally and segmentally. The injury may be lethal, resulting in necrosis or apoptosis, or it may be sublethal, resulting in structural and functional alterations that fall short of cell death. Overlap in the nephron segments affected by ischemia and nephrotoxins is possible, as is synergy in mediating damage, e.g. decreased RBF may lead to ischemic tubular injury in S3 segments, while also enhancing absorptive concentration of nephrotoxic antibiotics throughout the proximal convoluted tubule.

Initiation Phase – Consequences of Tubular Injury [38]

Tubular injury leads to an ATP-depleted state in tubular cells. Disruption of normal cytoskeleton, cell-cell contact at tight junctions, and loss of cell polarity with redistribution of Na-K-ATPase and other important proteins follows. At a biochemical level, cytosolic calcium levels rise and a variety of enzymes are abnormally activated. Ultrastructurally, cells appear swollen and microvilli are shed into the tubular lumen. Congestion of medullary capillaries is also a characteristic finding. Such alterations in the tubulointerstitial compartment leave it no longer adapted to water and solute transport or oxygen delivery, thus aggravating local ischemia and tubular injury. Some cells may suffer apoptosis or necrosis. A mixture of viable and nonviable cells is shed into the tubular lumen.

Accumulation of intraluminal debris and Tamm-Horsfall protein leads to intratubular obstruction. Impedance of urine flow in turn increases intraluminal and Bowman's capsular hydrostatic pressures, thus reducing GFR. In addition, transtubular backleak of filtrate occurs secondary to loss of cell-cell contact and sloughing of tubular cells. Hemodynamic alterations, intratubular obstruction, and transtubular backleak combine to produce the decline in GFR (Figure 2).

Maintenance Phase

The maintenance phase of ATN is characterized by persistence of renal failure, with GFR sometimes staying at its nadir for several weeks. Mechanisms thought to be responsible for sustained renal failure include toxic effects of reactive oxygen species generated as part of a reperfusion injury; persistent maladaptive

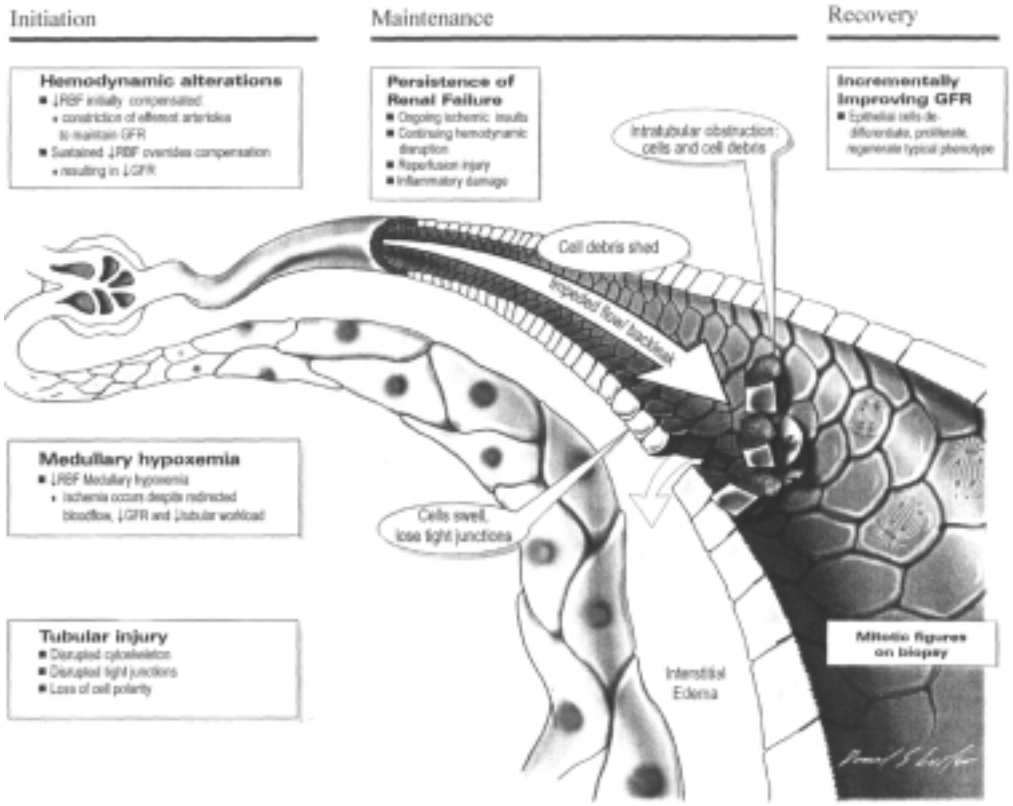

Figure 2. Mechanisms of reduced GFR in acute tubular necrosis.

intrarenal hemodynamic alterations; chemotaxis and adherence of neutrophils and platelets to intercellular adhesion molecules that have been unregulated on altered endothelial tissue; release by the leukocytic infiltrate of a mixture of damaging inflammatory mediators, proteases, elastases and other enzymes. Prolongation of ATN may also result from ongoing ischemic insults in dialysis-requiring ARF, due to inter- or intradialytic hypotensive episodes, combined with continued autoregulatory failure to maintain perfusion. The role of membrane biocompatibility in initiating inflammatory events that prolong ARF has received much attention recently. Finally, ongoing difficulties in maintaining adequate oxygen supply and in avoiding nephrotoxic exposures often complicate the course of a critically ill patient with ATN.

Recovery Phase

The recovery phase of ATN is characterized clinically by a diuresis followed by incremental improvements in GFR. At a cellular level, it is thought that some tubular epithelial cells dedifferentiate and recapitulate many of the processes involved in normal epithelial development in order to regenerate functionally intact tubules. Other cells may repair their cytoskeleton, cell-cell and cell-matrix interac-

tions and recover a normal functional phenotype. Mitotic figures are characteristically seen in biopsies at this time. The role of growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1) in regulating these processes is being investigated [35].

Management of ARF

The following discussion of management in ARF is broadly evidence based. However, it should be recognized that only a few studies in the clinical trial literature relating to management of ARF have prospectively randomized "like subjects" into control and study groups or been sufficiently powered to avoid missing clinically significant effects of the treatments being investigated. In this interpretation of current practices, areas of controversy are highlighted. Specific management strategies for vascular, glomerular, and interstitial processes giving rise to ARF are not discussed.

Principles of Management in Prerenal ARF

Treatment of prerenal ARF is directed towards restoring RBF and tissue oxygenation to normal as early as possible. For most patients restoration of renal perfusion is gratifyingly easy and rapidly effective. It is always necessary to address the underlying cause. Withdrawal of an NSAID or temporary withdrawal and reduction of diuretic dose may help in both the recovery and prevention of further prerenal insult. Avoidance of unnecessary exposure to other nephrotoxic agents, such as radiocontrast dye, while in a prerenal and, therefore, primed state for nephrotoxicity, is vitally important.

When volume depletion is the cause of prerenal azotemia, infusion of blood or saline is indicated, depending on the clinical circumstance. In edematous states complicating heart failure or liver failure, intravascular volume may also be low despite increases in total body salt and water. In general, volume expansion can be guided by careful serial clinical evaluations of volume status. However, in the critically ill patient with hypotension of unclear etiology, more precise definition of cardiac filling pressures and cardiac output may be required. In these cases, *right heart catheterization* is often employed to guide therapeutic decision making. Although the efficacy and safety of right heart catheterization has been demonstrated in certain subgroups of patients, a large observational study has recently questioned its safety for a significant proportion of critically ill patients in whom it is used [13]. As a result, there is a growing consensus (see comments published in JAMA regarding paper by Connors [13]) that the role of right heart catheterization needs to be studied by randomized clinical trials in those broad groups of patients for whom controversy surrounds its risks and benefits. In the interim, many believe the procedure to be a crucial diagnostic tool which, in the hands of operators experienced in its use and interpretation, can provide valuable information in the care of seriously ill patients.

Prevention or Reduction of Tubular Cell Injury

Given the high morbidity and mortality associated with ARF, prevention is crucial.

Strategies include maintaining an adequate intravascular volume; avoiding nephrotoxic exposure; saline expansion prior to, during, and after radiocontrast exposure in at-risk patients; titrating drug dosages to the level of renal function; understanding the vagaries involved in estimating GFR from serum chemistries in the elderly, the poorly nourished, and those whose blood chemistries are not in steady-state; and monitoring drug levels.

Restoration of RBF with early and active volume replacement may reduce renal tubular cell injury in the initiation phases of ischemic ATN. In nephrotoxic ATN, a forced saline diuresis may reduce the absorptive concentration of nephrotoxins in the tubular cells and renal interstitium, partly abrogating injury. This type of approach must always be tempered to the clinical situation with great care to avoid volume overloading critically ill patients or those with tenuous cardiac status.

Pharmacologic interventions with proven success in the prophylaxis of ARF are few. *Allopurinol* is beneficial as a pretreatment to chemotherapy in the prophylaxis of acute uric acid nephropathy following tumor lysis. *Mannitol* administered prior to clamp removal and reperfusion has been shown to be beneficial in improving postoperative graft function in kidney transplantation [62].

The prophylactic value of mannitol in other clinical settings is unproved. In fact, mannitol has been associated itself with causing ARF. *Furosemide* is also of doubtful prophylactic value, and its use may even negatively influence outcomes, as appears to be the case following radiocontrast exposure [58]. The strategies employed to reduce tubular cell injury in early and established ARF are similar to those used for primary prevention. No beneficial role has been demonstrated for either mannitol or furosemide in affecting the course or outcome of established disease. While uncontrolled data suggested a higher survival rate in patients who had an initial increase in urine output in response to furosemide, this observation was not upheld in controlled studies [11].

A controversial pharmacologic intervention in ARF is the use of *"renal-dose"/"low-dose"* dopamine to prevent the development of, or lessen the severity of, early or established ATN. To determine the utility of "low-dose" dopamine in preventing ATN, it has been estimated [17] that if the incidence of new onset renal failure in a study were 20%, then 400 patients would be needed for the study to have 80% power to detect a 10% risk reduction at the 0.05 level of statistical significance. Based on this observation, no study has ever conclusively addressed the primary preventative value of dopamine in ARF. The current evidence, such as it is, however, provides no substance to the claim that dopamine has a role in the prophylaxis of ARF in high-risk patients.

In those with early or established disease, good evidence for an effect is also lacking. In a small controlled study in ARF, it has been suggested that dopamine and furosemide were superior to furosemide alone [39]. However, this observation is hardly generalizable. A thorough review of papers in this area concluded that low-dose dopamine was apparently ineffective in humans in preventing ARF or improving outcomes in early or established ARF [17]. A post-hoc analysis of the Auriculin study group, which attempted to control for confounding factors and bias, also suggested that the use of low-dose dopamine confers no benefit in ARF [8]. As with primary prevention, however, a definitive clinical trial has not been done.

Dopamine is associated with documented significant complications, including tachyarrhythmias and myocardial ischemia. Experimental data indicate an implied risk also exists for selective mucosal ischemia in the gut, with

potential for enhanced bacterial translocation and subsequent systemic sepsis [56]. Use of *"low-dose" dopamine* has, up until recently, been very prevalent. This usage has been partly driven by the lack of other effective therapies and by a wealth of experimental evidence in animals suggesting that "low-dose" dopamine has beneficial effects on a variety of the factors involved in maintaining oxygen homeostasis in the renal outer medullary nephron segments. Justification of use of "low-dose" dopamine in patients, however, awaits a randomized, prospective, placebo-controlled clinical trial demonstrating both its safety and efficacy. The use of dopamine in pressor doses, with a view to protecting blood pressure and vital organ perfusion, remains clearly necessary and justified in some critically ill patients.

Atrial natriuretic peptide (ANP) is yet another agent of interest in early and established ATN. Through a series of mechanisms on transport processes and vascular smooth muscle tone, it has the potential to enhance GFR while sparing workload and oxygen demand in critically ischemic tubular segments. A recent well-designed prospective, randomized trial has reported on this agent in 504 critically ill patients with ATN [1]. Disappointingly, as compared with placebo, anaritide (a synthetic form of ANP) had no significant effect overall on the key outcome measures of need for dialysis, the rate of dialysis-free survival 21 days after treatment, and overall mortality. In the anaritide group, however, the subgroup of patients with oliguria had a reduced need for dialysis during the first 14 days and greater dialysis-free survival at 21 days. This type of subgroup analysis is hypothesis generating but does not constitute proof of benefit. In the case of anaritide, a follow-up randomized study in oliguric ARF has been terminated early because of failure to detect any benefit [3]. It remains to be seen whether specific patient groups or clinical settings can be identified in which this new drug will confer benefit.

Calcium channel blockers have been used with some success in ameliorating renal insufficiency in the short term after renal transplantation [11]. Whether this reflects a salutary effect on renal tubular cells of a decrease in cytosolic free calcium concentration, or is mediated by effects on renal perfusion or immune mechanisms is unclear. In transplantation, calcium channel blockers appear to be effective in reducing cyclosporine toxicity via the presumptive inhibition of cyclosporine-dependent vasoconstriction. It has also been suggested that inhibition of contrast-induced vasoconstriction by calcium channel blockers might be renoprotective. However, calcium channel blockers are potentially hypotensive agents. In general, they are neither routinely used nor believed to have a major role in the prevention or treatment of ATN.

General Supportive Therapy

From a *volume* standpoint, it is necessary to restrict salt and water intake in euvolemic patients with oliguric ATN to approximately 2 g and 1 L per day, respectively. This greatly limits space for alimentation or intravenous medications. It is particularly suited to situations in which rapid functional recovery and diuresis is anticipated. In the early stages of oliguric ATN, 1 – 2 high-dose intravenous therapies (80 – 400 mg) of furosemide may induce diuresis following adequate volume replacement. The goal of this therapy is to assist in volume management of the patient, not to favorably influence the course of the disease. In nonoliguric ARF, more liberal fluid intake replacing urine output and insensible losses to maintain a euvolemic state is advised.

The general inability of the kidney in ATN to handle excess free water and elaborate a hypotonic urine underlies the propensity in ATN toward development of *hyponatremia*. Avoiding excess intake of fluids low in effective osmolytes, such as water, dextrose, and hypotonic saline solutions, can prevent this. *Hypernatremia* is a less common development, which, in the absence of administration of hypertonic saline solutions, almost always implies a combined salt and water deficit that needs to be corrected.

Hyperkalemia often accompanies ARF and may be more exaggerated in settings of tissue breakdown, such as in rhabdomyolysis. ECG changes, e.g. QRS widening, p wave flattening and/or arrhythmias, are signs to provide intravenous calcium as a stabilizer to the myocardium. Insulin and dextrose infusions, intravenous bicarbonate, and, in selected patients, nebulized beta-agonists can be used to promote a shift of potassium into the intracellular compartment. Anion exchange resins and/or loop diuretics and/or dialysis serve to remove potassium from the body. Avoidance of drugs, such as ACE inhibitors, potassium-sparing diuretics, potassium supplements and beta-blockers together with dietary potassium restriction may help prevent hyperkalemia. *Hypokalemia* is less commonly seen in ATN but should be corrected carefully as it is independently arrhythmogenic, enhances the arrhythmogenicity of other drugs, e.g. digoxin, and may enhance the nephrotoxicity of aminoglycoside antibiotics.

Hyperphosphatemia is a frequent finding managed by dietary restriction and orally administered phosphate binders. Infrequently, hyperphosphatemia is severe enough to raise the calcium-phosphate product to a point where dialysis is required to prevent metastatic calcification. Magnesium-containing antacids are best avoided in ATN to prevent *hypermagnesemia*. Homeostatic alterations in the humoral control of calcium balance, i.e. low 1-25 dihydroxy-vitamin D_3 levels, PTH resistance, sometimes together with tissue uptake of ionized free calcium, as in pancreatitis or evolving rhabdomyolysis, may precipitate symptomatic *hypocalcemia* requiring the administration of intravenous calcium. *Hyperuricemia*, while generally present, is rarely of a degree requiring treatment. Levels greater than 15 mg/mL, however, raise the possibility of acute uric acid nephropathy and require treatment with allopurinol.

Finally, the accumulation of fixed acids and nitrogenous waste products from protein catabolism contribute to the development of an anion gap *acidosis* and other features of *uremia*. Complex acid-base perturbations may accompany the critically ill patient. Mixed disorders with retention of volatile and fixed acids and/or increased gastrointestinal bicarbonate losses can complicate respiratory and renal impairment in a surgical or medical patient and be particularly severe. Such disorders require careful monitoring and aggressive management. Ventilation and/or dialysis offer rapidly effective ways to raise pH in a patient with combined respiratory and metabolic acidosis. In the uncomplicated patient with ARF, short-term restriction of dietary protein intake to approximately 0.6 g/kg/day can retard the accumulation of protein catabolites. This is a very undesirable approach in the hypercatabolic patient in whom protein catabolic rates may exceed 200 g of protein / day.

Nutritional Support

Malnutrition is common in ARF. A hypercatabolic state results from: mediators of the systemic inflammatory response syndrome; metabolic and hormonal derangements, such as metabolic acidosis, insulin resistance, and

hyperparathyroidism; medications; and aggravating effects of uremic toxins. Compounding this, both inadequate nutritional supplementation and impaired utilization of nutrients can lead to profound protein-energy malnutrition [30].

Although nutritional supplementation is proposed to reduce morbidity and mortality, a beneficial effect in ARF has never been conclusively demonstrated. Nonetheless, attempting to supply adequate caloric and protein support to critically ill patients appears intuitively the correct approach. Enteral supplementation is preferable to parenteral treatment whenever possible. Provision of nutritional support can give rise to complications, including infections, volume overload, hyperglycemia, hypertriglyceridemia, hypokalemia and increases in uremic end products of protein metabolism. In oliguric ARF, nutritional support often requires support with complementary renal replacement therapy.

Prescriptions can be based on Harris-Benedict and Long equations [59]. Caloric requirements of 30 – 35 kCal/kg/day and protein requirements of 1.5 g/kg/day are not unusual. Protein is generally provided as mixed essential and nonessential amino acids, and lipids are used to supply 30 – 40% of total daily calories. In studies where the normalized protein catabolic rate (nPCR) has been measured, it has been noted to frequently exceed 1.5 g/kg/day and to vary intra-individually from day to day. Nutritional prescriptions based on equations that predict protein requirements may fall short of providing sufficient protein. Aggressive hyperalimentation with amino acids in a setting complicated by decreased utilization may, on the other hand, simply fuel urea nitrogen generation. Is it possible in profoundly hypercatabolic patients to individualize nutritional prescriptions and successfully override utilization difficulties such that a net even or positive nitrogen balance is obtained? Would it be beneficial to do this? Should nutritional supplementation be titrated to the protein catabolic rate calculated from urea nitrogen generation or total nitrogen appearance? Would this provide for better outcomes? What is the role of recombinant human growth hormone or insulin-like growth factor-1(IGF-1) in promoting an anabolic state and better overall outcomes in ARF? Answers to these questions are not readily available.

Renal Replacement Therapy (RRT)

Traditional indications for initiation of renal replacement therapy (RRT) in ARF include volume overload, hyperkalemia, severe metabolic acidosis, uremic complications such as pericarditis and encephalopathy, or simply treatment of a rapidly rising BUN and serum creatinine. It is often better to start RRT preemptively to make room for the obligate volume intakes incumbent in providing nutritional, antimicrobial, and pressor support to the critically ill patient than to await volume overload. Although peritoneal dialysis is still used and is an acceptable treatment in certain circumstances, most patients with ARF receive either intermittent hemodialysis (IHD) or one of the forms of continuous renal replacement therapy (CRRT) discussed later in detail. (Chapter II-1c).

For IHD, short femoral vein catheters are the least optimal access because they are accompanied by high recirculation rates and reduced clearances. Internal jugular vein catheters are preferred because they spare subclavian vein cannulation, thus avoiding the complication of subclavian vein stenosis, which can preclude future successful upper extremity vascular access. However, in the critically ill patient access comes at a pre-

mium, and one often must take what is available.

The value of *early* initiation of dialysis in ARF or *intensive* dialysis in ARF merits discussion. Current practice is to initiate hemodialysis at BUN levels ≤ 100 mg/dL. This is based on a series of historically controlled retrospective studies, over 2 – 4 decades ago, which suggested but did not prove in a statistically significant manner that early initiation of hemodialysis is better. For instance, in one series of 500 patients [33], the overall mortality decreased from 42 – 27% when patients dialyzed prior to 1968, with an average BUN of 164 mg/dL at initiation of dialysis, were compared to those dialyzed after 1968, when the average BUN at initiation of dialysis was 93 mg/dL. Similarly it was reported that mortality decreased from 77 – 51% when dialysis was begun at a BUN of 150 mg/dL rather than 200 mg/dL in patients with ARF [20].

In a prospective evaluation of different intensities of dialysis in the treatment of ARF in Vietnam War casualties [12], patients paired based on similar injuries were maintained with predialysis serum creatinine levels of 5 mg/dL or 10 mg/dL, respectively. Statistically significant differences were not present in the 18 patients. However, the mortality rate observed was 36% in the more intensively dialyzed group versus 80% in the other patients. Subsequently [24], no advantage for intensive dialysis was detected in a group of 34 patients, paired by ARF etiology, initiated on dialysis when serum creatinine increased to > 7.5 mg/dL and dialyzed to maintain predialysis serum creatinine of either ≤ 5 mg/dL or between 9 – 11 mg/dL.

Limitations of these studies need to be emphasized in terms of design and application to the type of ARF population managed in intensive care unit settings today. Current data on the value of earlier initiation or more intensive dialysis in critically ill patients are urgently needed. This is highlighted by a recent retrospective analysis in 842 patients with dialysis-requiring ARF, in which, adjusting for the Cleveland Clinic Foundation ARF scoring system (an index of severity), survival correlated positively with delivered dialysis dose across a broad range of severity scores [48].

Using models developed from calculating total nitrogen appearance (generation) over a 5 day period in a group of patients receiving CRRT, it has been predicted that some 50% of hypercatabolic ARF patients would require at least 6 intermittent hemodialysis treatments per week to maintain a peak predialysis BUN < 100mg/dL [9]. Large patients (> 90 kg) would predictably fail to achieve this target even with daily dialysis. In contrast, any number of the available modifications of CRRT can easily provide for this intensity of dialysis.

Choices between CRRT and IHD are generally made based on the hemodynamic stability of the patients, volume control issues, and local availability of resources and trained staff. In general in intensive care unit (ICU) patients with ARF, there is a group whose prognosis is so bleak that differences in the relative efficacies of currently available treatment modalities within the group may be small. Likewise in ARF that is uncomplicated, nonoliguric, and secondary to a single insult in an otherwise healthy patient, the prognosis may be equally good regardless of the dialytic modality chosen. However, there is a large intermediate group for whom differential cost-effectiveness data relating to CRRT vs. IHD is clearly needed.

Increased dialysis membrane biocompatibility in intermittent hemodialysis has been associated with improved recovery of renal function and a trend toward increased patient survival [27]. A second prospective study also found a lower survival rate in patients dia-

lyzed with nonbiocompatible cuprophane membranes [55]. Finally, a retrospective, nonrandomized analysis implicated membrane biocompatibility in outcomes in ARF [43]. However, a third prospective study did not confirm a difference in either the rate of recovery of renal failure or patient survival based on membrane biocompatibility [34]. This was a smaller study, and there were possible confounding differences between the 2 dialysis membrane groups in terms of the proportions of patients with diagnoses of ischemic ATN and nephrotoxic ATN.

Accelerating Renal Recovery

Specific treatments targeted at renal regeneration and enhancing recovery from ARF remain to be established into clinical practice. Among the general interventions, it is clear that ongoing exposure to triggering factors may prolong the maintenance phase of ATN. Avoidance of nephrotoxic insults and maintenance of euvolemia and organ perfusion are critical. Avoidance of dialysis membranes with poor biocompatibility profiles and/or hypotension during dialysis treatments may be important.

Managing Complications of ARF

Infectious complications account for a large proportion of the mortality in dialysis-requiring ARF. The patients are immunocompromised (by uremia and other comorbid conditions), hospitalized and have numerous assaults on normal mucocutaneous barriers. Careful attention to aseptic care techniques, surveillance for infectious complications, and early and aggressive management form the best lines of defense.

Bleeding is also a common problem. Qualitative and quantitative defects in circulating procoagulants and platelets may complicate the uremic syndrome and predispose to bleeding. Stress and hematologic complications of multiple organ system dysfunction contribute. Strategies to control and treat bleeding are as for any critically ill patient with the following added observations: 1 – 2 doses of intravenous desmopressin (DDAVP) 0.3 μg/kg may enhance clotting through the release of endothelial cell stores of von Willebrand factor; conjugated estrogens (0.4 mg/kg daily) have a slower but sustained procoagulant effect; aggressive dialysis without heparin can partly ameliorate the anticoagulant action of uremic serum; maintaining a hematocrit > 30% enhances clotting ability; and cryoprecipitate may also promote clotting in the uremic patient.

ARF – Specific Syndromes

Hepatorenal syndrome refers to a type of functional ARF, in the setting of hepatobiliary disease, that is characterized by a relatively hyperosmolar urine and a urine sodium concentration < 10 mM. Hepatorenal syndrome is a diagnosis of exclusion. Specifically there is a requirement to outrule prerenal, renal and postrenal etiologies. It occurs most often secondary to alcohol-induced hepatic cirrhosis but occasionally complicates the course of fulminant acute viral hepatitis, biliary tract obstruction or surgery, hepatic malignancies, and partial hepatic resections. Severe hepatic failure with ascites, jaundice, and encephalopathy usually accompanies this syndrome. The prognosis of hepatorenal syndrome is poor, with a mortality of 80 – 95%.

Survival is generally dependent on effective liver regeneration or liver transplantation. When liver function is restored by liver regeneration, liver transplantation, or by renal transplantation into a recipient with normal liver function, RBF and GFR return to acceptable levels.

Patients with advanced liver disease have an impaired capacity to generate urea and also have reduced generation of creatinine as a consequence of asthenia. Thus, in patients with liver disease significant renal impairment may be present with only borderline elevations in BUN and creatinine. The classic pattern of hepatorenal syndrome is that of an acute oliguric form with rapid onset and progressive renal failure. It is unclear, however, whether renal function is initially normal in such classic presentations. A commonly seen clinical presentation is the patient with advanced liver disease whose renal failure progresses more slowly over weeks or months, but otherwise fits the description of hepatorenal syndrome.

Hepatorenal syndrome is characterized by avid tubular reabsorption of salt and a FE_{Na} < 1%; by an intact urinary concentrating ability and a urine osmolality that exceeds the serum osmolality; by a bland urine sediment without increased cells or formed elements, and with no more than 1+ proteinuria. Other causes of prerenal disease can produce the same clinical picture. Differentiating between these often rests on a careful volume challenge with colloid and saline. Sometimes central venous pressure monitoring will be required to prevent volume overloading the patient. If tense ascites is present, the simultaneous relief of this by large volume or total paracentesis while infusing colloid is sometimes useful. Prerenal azotemia will respond to such maneuvers with a rapid recovery of function, whereas hepatorenal syndrome typically responds less favorably.

Glomerular pathology was universally present in a prospective series of 18 consecutive recipients undergoing native kidney biopsies at the time of liver transplantation for end-stage liver disease [16]. Abnormalities included minor changes, glomerulosclerosis, membranoproliferative glomerulonephritis, and IgA nephropathy. The significance of cirrhosis-associated glomerular pathology is unknown, and it is rare for glomerular disease to be a dominant feature of renal failure syndromes in advanced liver disease. In hepatitis C-infected patients, the presence of glomerular proteinuria or red cell casts may be indicative of an underlying membranoproliferative glomerulonephritis (MPGN).

The finding of granular and tubular epithelial cell casts in urine microscopy is not uncommon in patients with renal failure and liver disease. By clinical definition, these patients do not have hepatorenal syndrome but rather evidence of structural tubular damage, indicating ATN. The etiology of ATN in this setting may be nephrotoxic or a continuum of prolonged renal hypoperfusion resulting in ischemic renal injury consequent on the same pathophysiologic processes that lead to the hepatorenal syndrome. Initially the FE_{Na} may be < 1% when ATN complicates liver failure but increases to levels > 1% with time.

Hepatorenal syndrome is a multifactorial process. Hemodynamic changes with widespread peripheral arterial vasodilation, increases in arteriovenous shunting, and increased vascular capacitance accompany hepatic failure. Activation of the sympathetic nervous system and renin-angiotensin system is well documented. Evidence has accumulated implicating alterations in vasoactive substances, including nitrous oxide, endothelin and vasodilator and vasoconstrictor prostaglandins, both systemic and intrarenal, in advanced liver disease. The result is intense renal arterial and arteriolar vasoconstriction

Table 5. Causes of Rhabdomyolysis

Traumatic
Direct muscle injury
Nontraumatic
Increased energy consumption
Postexertional muscle injury
Postseizure injury
Heat stroke
Reduced energy production
Hereditary enzyme deficiencies
Ischemia
Diabetic ketoacidosis
Hypokalemia
Hypophosphatemia
Miscellaneous
Inflammatory myopathies
Infectious myopathies
Drugs
Sepsis syndrome
Toxins

with decreased RBF and GFR and a state of functional renal failure.

Continued preferential accumulation of ascitic fluid can be understood as a sequela of splanchnic vasodilation, portal hypertension, and low plasma oncotic pressures shifting Starling's forces to promote localization of free fluid in the peritoneal space. Refractory ascites in selected patients may provide an indication for transjugular intrahepatic portosystemic shunts, peritoneovenous shunts, or liver transplantation. Unfortunately, neither of the first 2 options appears to prolong survival in patients with advanced liver disease and refractory ascites [53, 60]. Both can be associated with serious complications. The decision to aggressively manage the patient with hepatorenal syndrome (including the provision of renal replacement) hinges on whether liver regeneration or liver transplantation is anticipated for a given patient. Short of one or the other of these outcomes, renal replacement may only prolong the dying process.

When candidates with hepatorenal syndrome are transplanted, increased hospital morbidity and length of stay, but comparable patient survival at one year and acceptable actuarial patient survival at 5 years (60% vs. 68%, $P < 0.03$ for patients with and without hepatorenal syndrome, respectively) has been described [26]. Recovery of dialysis independence was usual, and the incidence of ESRD after liver transplantation in patients who had hepatorenal syndrome was 7%, compared with 2% in patients who did not have hepatorenal syndrome.

Pigment-related Nephrotoxicity

Rhabdomyolysis is a syndrome characterized by muscle fiber dissolution and release of intracellular contents into the extracellular space and circulation. The occurrence of myoglobinuric ARF is common. It has been studied since the classic descriptions of the "crush syndrome" complicating the London bombing raids during World War II [6]. Hemoglobin, likewise a heme pigment, is also capable of precipitating ARF.

Muscles make up approximately 40% of body tissue and contain large quantities of myoglobin. A classification of the causes of rhabdomyolysis is listed in Table 5. Muscle hyperthermia accompanying strenuous physical exertion, convulsions, septic rigors, or malignant hyperthermia may precipitate rhabdomyolysis. Ischemic injury below a major arterial occlusion; inflammatory disorders such as polymyositis, and various hereditary and infectious muscle disorders have also been implicated. Many medications may mediate muscle injury, including cyclosporine

and HMG-CoA inhibitors increasingly used in combination in transplant patients. Alcohol can be implicated in the generation of traumatic and nontraumatic rhabdomyolysis. The latter is often due to hypophosphatemia during calorie refeeding, and is preventable with careful monitoring and phosphate supplementation. Hypokalemia is also described as causative for rhabdomyolysis.

Among the many etiologies of hemolysis/hemoglobinemia, those most likely to contribute to ARF combine rapid and extensive hemolysis with situations in which decreased renal perfusion may simultaneously coexist, e.g. disseminated intravascular coagulation (DIC), incompatible blood transfusions, and infectious causes of hemolysis such as malarial or clostridial infections. Hemoglobinuria appears to result in ATN only when associated with other systemic abnormalities, especially dehydration, shock, and acidosis.

Cellular ATP depletion, intracellular calcium overload, and myocytolysis characterize the events at a muscle cell level in rhabdomyolysis. Severe local capillary leakiness can lead to rapid widespread third spacing of fluid in the muscular interstitial spaces. The pathomechanisms of heme pigment-related ATN are shared by myoglobin and hemoglobin. Both pigments are filtered at the glomerulus, although hemoglobin much less freely than myoglobin because of its larger size (molecular weight 68 vs. 17 KD) and because of the presence of a hemoglobin-binding protein, haptoglobin, in the plasma. Intrarenal vasoconstriction is common as a consequence of uncorrected volume depletion due to third spacing of fluid. This vasoconstriction leads early on to a low FE_{Na} and a concentrated and acidic urine. In turn, this favors the precipitation of heme pigments and Tamm-Horsfall protein in the distal nephron with consequent intratubular obstruction. Delayed urine transit and reduced GFR prolong the exposure of proximal tubular cells to heme pigments and maximize pigment uptake by endocytotic absorption in the proximal tubule. Proximal tubular heme loading leads to cell injury by complex mechanisms in which ischemia, ATP depletion, and oxidant stress induced by intracellular release of catalytic iron molecules are all thought to play a role [63].

Because myoglobin is so much more freely filterable, the urine but not the plasma is pigmented in myoglobin-associated ATN, while both urine and plasma are pigmented in hemoglobinuric states. Heme-positive urine and the absence of red blood cells on sediment microscopy are characteristic findings. A definitive diagnosis can be made by demonstrating myoglobin or hemoglobin directly in the urine by counterimmunoelectrophoresis. In rhabdomyolysis, the diverse nature of the intracellular contents released into the circulation is reflected by marked elevations in plasma levels of creatine phosphokinase, phosphate, uric acid, potassium, and creatinine. The elevation in creatinine is more rapid than in other types of ARF, reflecting both muscle release and reduced plasma clearance. Thus, the BUN:creatinine ratio is typically < 10. Severe hyperkalemia may be seen. The release of intracellular potassium and phosphorous can obscure the pathogenic role that low levels of these electrolytes may play in the etiology of the condition. Symptomatic hypocalcemia due to high phosphorous levels and deposition in muscle beds is common. In the recovery phase of myoglobinuric ARF, hypercalcemia may be seen as a consequence, in part, of calcium mobilization from skeletal muscle.

The prevention of rhabdomyolytic-induced ATN rests on early and aggressive volume replacement, enhancing the rapid clearance of heme pigments, and providing protection to proximal tubular cells. Retrospective analyses provide overwhelming support for aggressive

volume replacement. When urine output allows, it has been recommended that after resuscitation at least a 12 L mannitol-alkaline diuresis be provided in the first 24 hours [2]. To provide for this, large volumes of fluid may be required early on to replace the third-spaced volume loss. Alkalinization is recommended to produce a urine pH > 6.5. This prophylactic measure aims to reduce Tamm-Horsfall-heme pigment precipitation, which occurs more readily in an acid urine – although it may simply exert its protective effect through a saline diuresis. Mannitol probably exerts its protective beneficial effect as a proximal tubular diuretic rather than the theoretical suggestions that it has a beneficial vasodilatory effect or hydroxyl radical scavenging effect. The emphasis is on maintaining a volume-replete state and a solute diuresis with an alkaline urine. If mannitol is used, monitoring is mandatory to avoid an excessively hyperosmolar state. The amount of bicarbonate required to produce an alkaline urine varies widely. We prefer to administer the bicarbonate as part of an isotonic solution (0.45% saline solution with 75 mmol $NaHCO_3$), because bolus doses of hypertonic bicarbonate predispose to hypernatremia. Once renal failure is established, these interventions are of no benefit, and the principles of management are the same as for any form of ATN. Avoidance of volume overload then becomes mandatory, and it should be remembered that pigment-induced ARF may often be accompanied by severe hyperkalemia, hyperphosphatemia, and hypocalcemia, which can necessitate early dialysis.

Radiocontrast Procedures and ARF

ARF after radiocontrast-related procedures is a common problem in the inpatient setting.

The importance of ARF after radiocontrast procedures in an in-patient hospital population was recently emphasized in a well-controlled retrospective cohort analytic study [36]. In this analysis, the development of renal failure after a radiocontrast procedure was strongly and independently correlated to mortality risk in a multivariate analytic model developed and validated for the cohort being studied. Over 16,248 patients were screened to identify 183 index subjects who developed ARF (1.1% of those undergoing radiocontrast-related investigations). The overall mortality rate was 34% vs. 7% in those who did or did not develop ARF, respectively. The study did not firmly establish contrast nephropathy as the underlying etiology of ARF in all the observed cases. However, the results do pertain to an at-risk inpatient population undergoing contrast procedures and, as such, are important.

Atheroembolic disease complicating angiographic procedures is discussed elsewhere. This next section focuses on the outcome and clinical significance of classic cases of contrast nephropathy. The classic presentation of contrast nephropathy is that of deteriorating renal function occurring within 1 – 2 days, peaking within 3 – 5 days, and resolving within 7 – 10 days of radiocontrast exposure. Most cases are nonoliguric and do not require dialysis. The urine sediment early in contrast nephropathy may be bland, and urinary indices suggest prerenal injury (low FE_{Na}). Later, tubular epithelial cells and granular and tubular epithelial cell casts are seen, indicating tubular injury. The mechanisms of contrast nephropathy are thought to involve a reduction in RBF, an imbalance between tubular workload and oxygen supply, and a direct tubular toxicity of the contrast agent.

Contrast nephropathy occurs in only approximately 3% of patients without identifiable risk factors in most large prospective

population studies. With appropriate controls, the true incidence of ARF in low-risk patients (nonazotemic, nondiabetic) is even less: 2.1% and 1.3% in those exposed and not exposed, respectively, to contrast media [14]. Preexisting chronic renal impairment, diabetes, and multiple myeloma are the comorbid risk factors most often cited as predisposing to contrast nephropathy. Whether preexisting renal insufficiency truly increases the incidence of contrast nephropathy or simply increases the sensitivity of detecting renal injury as a result of the exponential relationship between creatinine and GFR is debatable. It is clear, however, that contrast nephropathy is more of a problem in those with impaired baseline kidney function. For example, the implications of a 10 mL/min decrease in GFR are different for the patient with a baseline GFR of 20 mL/min, compared to a patient with a baseline GFR of 120 mL/min. The incidence of contrast nephropathy appears directly proportional to the degree of chronic renal insufficiency. Moore et al. report an incidence of 4.7%, 14.3%, and 20%, respectively, for those with baseline creatinine levels in the ranges of 1.5 – 1.9, 2.0 – 2.4, and 2.5 – 2.9 mg/dL, respectively [44].

Table 6. Toxins, Drugs and Acute Tubular Necrosis

Radiocontrast
Heme pigments
Immunoglobulin light chains
Platinum/Mercury/Chromium/Uranium/Bismuth/Silver
Organic solvents
Aminoglycosides
Amphotericin B
Penicillins/Cephalosporins/Imipenum
Vancomycin
Ifosfamide
Interleukin-2
Cyclosporine/FK506
Intravenous immune globulin
Streptozotocin
Mannitol

Having diabetes and chronic renal insufficiency seems to further predispose to more clinically serious contrast nephropathy. Risk is again proportional to baseline GFR, and of those with severe chronic renal impairment 50 – 90% may develop contrast nephropathy. For some, the ARF will be irreversible. In contrast to azotemic diabetics, diabetics with normal renal function are not at a significantly increased risk for contrast nephropathy, according to recent studies. Likewise, multiple myeloma in the absence of other predisposing risk factors (e.g. volume depletion, renal insufficiency) does not absolutely mitigate against contrast exposure [42]. It is wise, however, to be careful with all diabetics and patients with multiple myeloma, regardless of baseline serum creatinine levels. Any prerenal state, whether or not functionally significant prerenal azotemia has been documented, should be considered an at-risk state for contrast-induced renal injury. To better appreciate the procedural risk, it is prudent to recommend a recent serum creatinine precontrast exposure for all inpatients and for outpatients who are elderly, diabetic, hypertensive, or predisposed to decreased renal perfusion.

Prophylaxis of contrast nephropathy is important. Indications for contrast-related procedures need to be clearly defined, especially for high-risk patients. Measures should be taken to correct predisposing factors such as volume depletion. Optimal prophylaxis includes avoidance of concomitant nephrotoxic exposures and ensuring a euvolemic state. Maintaining a saline hydration, with 0.45% saline solution, 1 mL/kg body weight/hr, commenced 12 hours before and maintained for 12 hours after contrast exposure is indicated for at-risk patients. In a randomized,

prospective study, saline alone provided better protection against acute contrast-induced decreases in renal function than saline combined with either mannitol or furosemide [58]. The prophylactic usefulness of other agents in high-risk patients remains uncertain. However, the volume of contrast to which the high-risk patient is exposed should be minimized [40]. Likewise, low-osmolality contrast media has been shown in a large, prospective, randomized trial to reduce the incidence of contrast nephropathy in azotemic patients with and without diabetes [54].

Drug-related ARF

See table 6 for summary.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs can lead to decrements in GFR and elevations in BUN and serum creatinine when used in clinical circumstances characterized by prostanoid-dependent RBF. The pathomechanism is clearly hemodynamic. NSAIDs do not exert this effect in euvolemic individuals with normal renal function because in this state, maintenance of RBF and GFR is independent of prostaglandins.

A decline in absolute or relative effective arterial blood volume results in compensatory humoral mechanisms to maintain blood pressure. As in most hormonal systems, these vasoconstrictor hormones participate in a negative feedback loop by promoting the renal production of vasodilatory substances, primarily prostaglandins. Intrarenal prostaglandins work both to modulate vasoconstriction by lessening preglomerular vascular tone, thus preserving GFR, and to preserve medullary oxygen hemostasis by preferentially increasing medullary regional perfusion. NSAIDs inhibit the cyclooxygenase (COX) I and II isoenzymes that metabolize arachidonic acid substrate in a rate-limiting step in prostaglandin synthesis. In states of diminished effective arterial blood volume, they inhibit the protective effects of prostanoid on RBF. The consequence is ARF with rising BUN and creatinine levels, sodium and water retention, and frequent hyperkalemia. Onset is typically within 24 hours of taking a dose. The effect occurs with all commonly used anti-inflammatory drugs at therapeutically prescribed doses. Low-dose aspirin for platelet inhibition does not produce the effect. Sulindac is an NSAID which the kidney can rapidly metabolize and inactivate. However, acute hemodynamic renal failure has also been described with this drug. In addition to leading to ARF, NSAIDs produce other nephrotoxic effects including an allergic interstitial nephritis (of slow onset) and nephrotic syndrome secondary to minimal change disease (MCD) or membranous glomerulonephritis. In the future, selective Cox II inhibitors will be available and may mediate anti-inflammatory effects at doses that minimally alter intrarenal hemodynamics [23].

Angiotensin-converting Enzyme (ACE) Inhibitors

In discussing drug-induced hemodynamic ARF, it is necessary to comment on ACE inhibitors and angiotensin II (Ang II) receptor blockers. These 2 classes of drugs are associated with predictable declines in GFR in patients with chronic renal insufficiency or humoral-dependent RBF, especially in patients

with bilateral renal artery stenosis. In these circumstances autoregulatory mechanisms protect GFR by preferential Ang II-mediated postglomerular arteriolar constriction. Loss of this increased efferent arteriolar tone follows introduction of any of the drugs belonging to these 2 classes of agents. The decline in GFR is generally acceptable as a hemodynamic and reversible consequence. Indeed, it is desirable in order to slow subsequent progressive declines in GFR in macroproteinuric renal diseases and diabetes. However, severe baseline renal failure and hyperkalemia are limiting factors to the use of these agents. Very rarely, ARF may result from ACE-associated renal infarction. This occurs in patients with severe baseline renovascular disease in whom abrupt hypotensive effects of drug administration drop the perfusion pressure across a tight renal artery stenosis and precipitate complete renovascular occlusion. Although rare, this occurrence dictates caution in using these agents in patients with suspected severe renal artery stenosis.

Antibiotics

Aminoglycosides have a major role in the treatment of gram-negative microbial infections. They are small molecules (approximately 500 KD), negatively charged, minimally protein-bound in plasma, and excreted unchanged in the urine. Their plasma clearance roughly equals GFR. After filtration in the kidney, reuptake of a small percentage of aminoglycosides in the proximal tubule is mediated via the process of adsorptive pinocytosis. Once intracellular, the pinocytosed vesicle fuses with lysosomes and localizes the aminoglycosides to this organelle. The intracellular half-life of an aminoglycoside is up to 4 – 5 days in the renal cortex vs. a plasma half-life that is measured in hours. Accumulation of high concentrations of the drug occurs in proximal tubular cells.

The nephrotoxicity that complicates some 10 – 20% of courses of aminoglycoside antibiotics is the result of this accumulation. The aminoglycosides interfere with lysosomal phospholipids leading to a so-called "phospholipidosis" characterized in part by intracellular accumulation of myeloid bodies that contain aggregates of undigested phospholipid membranes damaged by the aminoglycosides. Other drugs may cause phospholipidosis without causing renal failure. At what point and through what additional mechanisms aminoglycosides mediate their nephrotoxicity needs further clarification.

The consequences of aminoglycoside toxicity are proximal tubular cell injury with enzymuria and the shedding of microvilli and cells into the tubular lumen. Intraluminal obstruction and transtubular back leak are important pathophysiologic mechanisms. Serum creatinine and BUN levels characteristically rise 7 – 10 days into a course of aminoglycoside treatment. In uncomplicated cases where aminoglycosides represent the sole insult to the kidneys, cessation of the antibiotic typically is followed by a course of nonoliguric ARF, not requiring dialysis intervention, with a gradual recovery of renal function over a couple of weeks. However, a more common situation is the additional contribution of aminoglycosides to renal failure in combination with other renal insults, including ischemia, contrast agent and sepsis. The relative contribution of aminoglycosides in this setting is more difficult to establish.

While the therapeutic indications for aminoglycosides have been clearly established over time, the avoidance of nephrotoxicity remains a challenge. Advanced age, preexisting renal disease, liver disease, long or repeated courses of antibiotic, volume depletion and/or a prerenal state, hypokalemia, hypo-

magnesemia, and concurrent exposure to additional nephrotoxic agents predispose to aminoglycoside nephrotoxicity. Avoidance of some of these predisposing factors, such as volume depletion, is possible. Consideration may be given to shorter courses when antibiotic sensitivities are available to guide treatment.

Dosimetry pertaining to aminoglycosides is another area of active research. The bactericidal effect of aminoglycosides correlates with the peak blood level achieved, while the nephrotoxic side effect correlates with trough blood levels. As 100% of the drugs are renally cleared, preexisting or developing renal failure during a course of aminoglycosides will lead to increasing plasma trough levels unless the dosage interval is appropriately lengthened to allow for clearance. The widespread use of measuring serum concentrations of aminoglycosides has been disappointing in terms of its impact on the incidence of nephrotoxicity. This is not to say that measurement of levels and avoidance of high trough levels should be ignored, but rather emphasizes that nephrotoxicity may occur even when levels are maintained in the appropriate range.

Daily dosing of aminoglycosides in patients with normal renal function was introduced a number of years ago to exploit several known properties of this class of drugs, namely that bactericidal effect correlates with peak drug levels, that a post-antibiotic effect is present suppressing bacterial growth at levels below the minimal inhibitory concentration (MIC), that the length of the post-antibiotic effect increases with higher peak levels of the drug, and that adsorptive pinocytosis in the proximal tubule is a saturable process. It was hoped that once-daily dosing would enhance or sustain efficacy while reducing the incidence of nephrotoxicity. Recommendations have been published for high-dose, extended-interval aminoglycoside regimens including dose adjustment guidelines for those with creatinine clearances in the range of 20 mL/min to normal [46, 50]. At present there is moderate to strong evidence of probable clinical benefit for daily dosing in gram-negative infections; moderate evidence of a limited benefit or no difference in gram-positive infections; little or no evidence for benefit in pediatric, geriatric, pregnant, obese, burn, or cystic fibrosis patients, or in those with creatinine clearances < 20 mL/min; and indications that high-dose extended interval regimens may be inappropriate for enterococcal infections [22]. The application of computer-generated alert systems may also have a role in reducing the incidence or severity of drug-related nephrotoxicity [52].

Amphotericin B Nephrotoxicity

Amphotericin B, a polyene antibiotic, presently remains the most effective agent for the treatment of deep-seated and disseminated fungal infections. Amphotericin B interacts with lipid sterols present in the outer membranes of susceptible microorganisms. Fungi contain ergosterol as part of their membranes, hence their sensitivity to polyenes such as amphotericin B. In contrast, bacteria do not have lipid sterols in their membranes and are resistant to the effects of this class of drug.

The renal toxicity of amphotericin B is characterized by distal renal tubular acidosis (RTA), hypokalemia, an ADH-resistant urinary concentration defect, reduced GFR, and occasional symptomatic hypomagnesemia and salt wasting. The integration of amphotericin B with cell membranes in the distal nephron leads to formation of pores of sufficient size to allow abnormal solute trafficking. The distal RTA is believed to be secondary to an increased passive permeability of the luminal membrane and back diffusion of hydrogen

ion, rather than an active transport failure. Likewise, potassium wasting, which may be profound, occurs in the context of increased membrane permeability in the distal nephron and passive flux along a favorable electrochemical gradient. Increased aldosterone-dependent potassium-sodium exchange is not involved. Although the hypokalemia may aggravate or cause a nephrogenic diabetes insipidus, membrane effects increasing the permeability of the medullary collecting ducts to urea may partly efface the medullary hypertonicity gradient and account for some of the failure to elaborate a concentrated urine. Hypomagnesemia occurring as a result of amphotericin B toxicity may contribute to exaggerated hypokalemia that is resistant to aggressive correction until the magnesium has first been replaced.

In contrast, acute rises in serum potassium levels have been described following the rapid infusion of amphotericin B in anephric patients [15]. This may occur because of leakage of potassium from the intracellular compartment unopposed by exaggerated urinary losses. The patient with established renal failure receiving amphotericin B needs to be carefully monitored for this complication.

Pathologic mechanisms by which amphotericin B precipitates ARF include both a renal vascular effect producing ischemia and direct tubular toxicity. Greater levels of toxin in the kidney caused by longer courses of treatment and/or larger doses overwhelm the ability of the cell to repair membrane defects. The renal toxicity is clearly dose dependent. While GFR can return to normal after discontinuation of the drug, a fraction of patients have irreversible damage. Chronic renal failure was observed in 44% of patients receiving a total dose of > 4 g and in 17% of patients receiving < 4 g total dose [5].

Preventive strategies include salt loading and avoidance of concomitant volume depletion and additional nephrotoxic insults. Protective roles for alkalinization, aminophylline administration and calcium channel blockers remain unproved. A small prospective study showed no beneficial effect of mannitol, while a case control study reported a 12.5 fold greater risk of nephrotoxicity with prophylactic use of furosemide. The place of liposomal and other lipid-based formulations of amphotericin B requires continued investigation. An advantage proposed for these formulations is a reduction in nephrotoxicity based on characteristics that favor selective drug delivery to the reticuloendothelial system, macrophages, and sites of infection. These formulations also decrease the systemic side effects that often accompany the infusion of free amphotericin B.

Miscellaneous Antibiotics

Other antibiotics implicated in the generation of ATN include the beta-lactam group of antibiotics, i.e. penicillins, cephalosporins, and imipenum. Except for cephaloridine, nephrotoxicity is a rare side effect of these drugs. The mechanism of injury may be via lipid peroxidation in the case of cephaloridine, or mitochondrial injury in the case of the other antibiotics. Selectivity for the proximal tubule is a result of dependence on the organic amino acid transport system. The administration of imipenum with cilastin serves to reduce its toxicity, because cilastin inhibits enzymatic cleavage of imipenum by brush border dehyropeptidases in the proximal tubule. The nephrotoxicity of current vancomycin preparations is much less than before, and synergistic nephrotoxicity between these preparations and aminoglycosides has not been convincingly demonstrated. Tetracyclines may worsen azotemia via an antianabolic effect leading to an elevation in BUN, but not

serum creatinine, in patients with preexisting azotemia. Accumulating levels of tetracycline may also produce a toxic tubular cell injury in patients with liver disease. Acute allergic interstitial nephritis complicating antibiotic usage is not discussed here.

Antineoplastic Drugs and Heavy Metals

A variety of heavy metals have been shown to produce ARF with proximal tubular cell necrosis. Salts of mercury, arsenic, chromium, uranium, bismuth, silver, and platinum are potent nephrotoxins. Exposure is usually occupational with the exception of the platinum salts, which are used therapeutically.

Cisplatin, which describes the organic compound cisdiaminodichloroplatinum, is a chemotherapeutic agent. Its nephrotoxic effect is dose limiting. Interventions that decrease nephrotoxicity are potentially beneficial in terms of facilitating larger doses and greater efficacy. After a single dose of cisplatin, mild reductions in GFR may be seen in up to 25% of patients. Repeated doses may give rise to nephrotoxicity in up to 75% of patients. While the acute effects are generally reversible, permanent irreversible damage may follow repeated exposure. The reduction in GFR is generally delayed 1 – 2 weeks after dosage. The mechanism is understood to depend on uptake and slow transformation of cisplatin in proximal tubular cells. Aquation of the cis chloride sites of cisplatin in the relatively "low chloride" intracellular environment is thought to produce toxic-charged species. The typical histologic features are injury in the tubulointerstitial compartment. Particularly susceptible are the S_3 segments of the proximal tubule, and less so the distal tubule and collecting duct.

Enzymuria, rarely measured in clinical practice, may be the earliest indication of tubular injury. Following on this, urinalysis findings of tubular proteinuria and granular and tubular epithelial cell casts are seen. Hypomagnesemia complicates 50% of cases. Urinary magnesium wasting may contribute to secondary hypokalemia and hypocalcemia. This defect typically resolves within a few weeks of the last cisplatin dose, but has been observed to persist for several years.

Prevention of cisplatin nephrotoxicity is approached by employing an aggressive saline diuresis and also by avoidance of concurrent exposure to other nephrotoxic drugs, such as aminoglycosides. In general, a euvolemic state is required, after which a bolus dose of saline of approximately 500 mL and infusion of as much as 150 – 250 mL per hour thereafter is initiated before, continued throughout, and for 4 – 6 hours after cisplatin has been infused. Normal saline or hypotonic half-normal saline has been used with or without mannitol. It has been observed that larger doses of cisplatin remain nephrotoxic despite these measures, but can be tolerated when administered in hypertonic (3%) saline solutions. This raises the possibility that optimal protection requires not just hydration with increased urine flow and reduced contact between tubular cells and the drug, but an additional chloriuresis and hyperchloremic state. Continued investigation of other agents that might reduce nephrotoxicity is worthwhile. With careful application of a prophylactic hydration protocol, renal toxicity is no longer per se a treatment limiting complication of cisplatin chemotherapy. Other chemotherapeutic platinum analogues have been developed, including carboplatin and ormaplatin. Renal dysfunction has been described with both, and hydration is important when using these drugs.

Other Antineoplastic Drugs

The alkylating agent *ifosfamide*, unlike its parent compound cyclophosphamide, is associated with nephrotoxicity. It also shares with cyclophosphamide the property of urotoxicity. Mesna, a synthetic sulfhydryl compound, protects against the urotoxicity of the acrolein and chloroacetalalahyde metabolites of ifosfamide, but it does not protect against the renal parenchymal insult [57]. Ifosfamide nephrotoxicity is characterized by proximal tubule cell injury and Fanconi's syndrome with proximal RTA, phosphaturia, glycosuria, uricosuria and aminoaciduria. Aggressive supplementation of electrolytes may be necessary, and in children a propensity to hypophosphatemic rickets has been described. While GFR is generally only mildly reduced, severe ARF may also occur. Preexisting chronic renal insufficiency or prior cisplatin exposure may be a predisposing factor to ifosfamide-induced renal injury. General preventive measures are advisable. Experimental data has suggested glycine, via a membrane protective effect, is worth investigating as an agent with potential clinical applications.

Recombinant *interleukin-2* is employed as an immunomodulatory agent in various drug protocols for patients with metastatic adenocarcinoma. A lymphokine normally produced by activated T-cells, it is sometimes given in combination with lymphokine-activated killer cells. A predictable septic shock-like syndrome often follows its administration, with decreased systemic vascular resistance, increased cardiac output, capillary leakiness, and a transient requirement for crystalloid, colloid, and/or pressors to maintain perfusion pressure. Weight gains of 10 – 15% of body weight are not unusual. The renal lesion most commonly seen is a prerenal functional azotemia with characteristic urinary indices and rapid reversibility with restoration of RBF. Ischemic ATN may complicate its use. Rare cases of allergic interstitial nephritis and even RPGN have been described.

Nitrosureas associated with renal toxicity include streptozotocin, semustine, and lomustine. Of these, streptozotocin is the most likely to manifest acute toxicity. Fanconi's syndrome, mild reductions in GFR, and severe acute "nephrotoxic" ATN have all been described.

Mitomycin-C is notorious for the propensity for recipients to develop HUS as a delayed and dose-related complication of this drug. HUS is considered elsewhere in this text.

The drug *mithramycin-C* used occasionally to treat hypercalcemia of malignancy is associated with ARF when used as an antineoplastic agent. ARF, however, is rare when single doses are used to treat hypercalcemia, although it has been reported.

Gallium nitrate, another agent used to treat hypercalcemia of malignancy, may lead to ARF as a result of intratubular precipitation of calcium-gallium-phosphate salts. This was a major side-effect of short infusions of this drug in initial studies. Continuous infusions (200 mg/m^2 for 5 days) have been administered without severe nephrotoxicity.

A similar mechanism of intrarenal obstructive ARF is described with large doses of *methotrexate*. Intraluminal precipitation of the metabolite 7-hydroxy-methotrexate and methotrexate is favored by a concentrated acidic urine. Preventive strategies employing hydration, alkalinization, and folinic acid (to prevent systemic toxicity) generally work well. Low-dose chronic use of methotrexate is generally well tolerated. However, renal impairment can lead to significant drug accumulation and systemic toxicity.

Mannitol

Mannitol is the polyol of the sugar mannose. Administered intravenously, it is inert, remains in the extracellular compartment, and is freely filtered by the kidney. It is used clinically for its osmotic properties to reduce intracranial pressure and intraocular pressure, and occasionally for its diuretic properties. It has been used as prophylaxis for nephrotoxic ATN, although an incremental benefit of mannitol over and above that gained from solute diuresis is unproved. When mannitol infusion exceeds its rate of clearance, the drug accumulates in the extracellular space. The osmotic effects are exaggerated beyond the therapeutic targets of lessening intracerebral pressure to include excessive cellular dehydration and altered mental status, extracellular volume expansion with congestive heart failure (CHF) and pulmonary edema, and metabolic abnormalities such as hyponatremia, hyperkalemia, and metabolic acidosis. Less recognized is the potential for mannitol to paradoxically precipitate ARF [18].

Observations have connected hemodynamic effects of mannitol at high and low doses with worsening medullary hypoxemia. Therefore, injury is most likely secondary to ischemia. A dose of 0.25 mg/kg every 4 hours used to lower intracranial pressure appears to be therapeutically effective, and higher doses have been shown to portend a poor prognosis. The osmotic gradient between the extracellular and intracellular compartment attributable to mannitol determines the fluid shift. It is recommended that during mannitol use, the osmolal gap rather than the serum osmolality be monitored. This is because a serum osmolality of 310 mOsm/kg in the setting of a sodium of 140 mM indicates a very different mannitol concentration in the extracellular fluid than the same serum osmolality in the setting of a sodium of 120 mM. ARF has been observed with peak osmolal gaps of 74 ± 39, and 107 ± 17 mEq/kg. The osmolal gap should be prevented from reaching these high levels by decreasing or holding mannitol doses while following renal function closely. ARF-complicating mannitol infusion reverses rapidly when the drug is discontinued.

Immunosuppressive Drugs

Nephrotoxic effects of immunosuppressive drugs are discussed in detail elsewhere in this text. Briefly, both cyclosporine and tacrolimus (FK506), commonly used immunosuppressants, can contribute to acute elevations in BUN and serum creatinine in a number of ways. First, both produce dose-dependent intrarenal preglomerular vasoconstriction with a reduction in glomerular hydrostatic pressure and GFR. This effect occurs within the therapeutic dose range used for transplantation. Second, nephrotoxic effects on both microvasculature and tubules are described. Early posttransplantation endothelial injury can initiate a thrombotic microangiopathic syndrome with ARF. This is fortunately uncommon. Acute tubular toxicity early post-transplant is also a dose-related adverse effect. Both cyclosporine and FK506 produce a chronic arteriolopathy and chronic toxicity with irreversible kidney damage that is discussed in detail elsewhere (Chapter III-4).

ARF in Bone Marrow Transplantation

Up to 40 – 50% of patients receiving a bone marrow transplant may develop some degree of ARF. Often dialysis is required, and the mortality rate is as high as 80 – 90%. A variety of etiologic factors, singly or in combination, may play a role. Included are volume deple-

tion; exposure to nephrotoxic antineoplastic, antibiotic, or immunosuppressive drugs; and an acute uric acid nephropathy complicating cytoreduction therapy. Additional etiologies include a syndrome of functional renal failure, hepatorenal syndrome-like in its presentation, that accompanies veno-occlusive disease of the liver. It is primarily a hemodynamic renal failure that occurs coincident with veno-occlusive disease during the first 2 – 3 weeks after transplantation. The outcome of the ARF is dependent on the outcome of the veno-occlusive disease. In the past, myohemoglobinuric ARF was seen to complicate marrow transplantation. This was usually the result of red cell lysis and hyperthermia complicating the use of dimethyl-sulfoxide as a cryoprotectant. Autologous and allogenic marrow is now red cell depleted, and patient management is specifically designed to avoid volume depletion. As a result, pigment nephropathy is now rare. Tumor infiltration is a recognized but exceedingly rare cause of ARF. For instance, although autopsy studies report a prevalence of 63 – 90% renal infiltration in chronic lymphocytic leukemia (CLL), reports of impaired renal function are uncommon.

Tumor Lysis Syndrome

Tumor lysis syndrome is characterized by ARF complicating the release of large quantities of intracellular molecules by necrotic tumor cells. It occurs most often in non-Hodgkin's lymphoma and acute lymphocytic leukemia (ALL). These are tumors with large bulk and very rapid growth phases. The syndrome can occur without treatment as tumors outgrow their blood supply, or it may complicate glucocorticoid or cytoreductive therapies. Characteristic metabolic abnormalities are hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute, typically oliguric renal failure. Volume depletion often plays a predisposing role. Renal failure is due to intraluminal precipitation of crystals of uric acid and, to a lesser extent, calcium phosphate. This occurs in the distal nephron leading to intraluminal obstruction. Precipitates and sludging are also seen in the medullary microvasculature.

Hydration, high-dose allopurinol, and alkalinization attenuate the occurrence and severity of this syndrome. Prevention is not absolute. Alkalinization to reduce uric acid precipitation should be titrated to achieve a urine pH of 7.0. If the urine pH rises above 7.0, alkali should be held because an alkaline urine favors calcium phosphate precipitation. Due to the scale of release of potassium and phosphorous from intracellular stores, early and intensive dialysis is frequently needed to prevent life-threatening hyperkalemia and extensive metastatic calcification. Early dialytic support can be life saving. Renal function typically recovers well in patients who survive.

Future Directions

A recent publication resulting from an NIH consensus conference, organized to discuss future directions for research in ARF, included recommendations for establishment of a multicenter database to be developed to facilitate outcomes research in ARF; an emphasis on prospectively validating risk stratification measures in ARF to be employed in the design of new randomized clinical trials; new clinical trials in ARF to investigate the roles of low-dose dopamine, hemodynamic monitoring, nutritional supplementation, di-

alysis modalities, dialysis delivery/intensity, and new adjunctive agents developing out of basic science research; and enhanced support of basic research addressing the cellular and molecular basis of renal tubular injury, changes in cell differentiation, cell repair, cell death, and organ recovery [19]. These various goals address urgent needs of physicians, patients, and families when approaching difficult decisions in the management of patients with ARF.

Exciting new treatments need to be investigated. Experimental data are accumulating to suggest exogenous administration of epidermal growth factor (EGF), hepatocyte growth factor (HGF), or insulin-like growth factor-I (IGF-1) might be beneficial in ARF syndromes [35]. Effects of growth factors are likely to be directly exerted on tubular cells. IGF-1 is also anabolic and modulates blood flow to increase RBF and GFR. In a double-blind, placebo controlled, prospective, randomized study of patients undergoing suprarenal aortic or renal artery surgery, the administration of IGF-l was found to be feasible and associated with a smaller postoperative decline in renal function [21]. However, no cases of established ARF were documented in the study, and the use of IGF-l did not significantly impinge on the outcomes or hospital course. IGF-l has also been safely administered to patients with chronic renal failure, where it augments RBF and GFR. The therapeutic value of arginine-lysine-aspartate (RGD) peptides is also worth investigating [25]. These peptides bind up B1 integrins on tubular cells, thus preventing the cells from binding to each other. They may also ameliorate aggregation of intraluminal debris and cells, thus preventing luminal obstruction in ATN. Antibodies against the cell adhesion molecule ICAM-l or against other inflammatory mediators may reduce the inflammatory component of the ischemic-reperfusion injury in the maintenance phase of ATN [31]. Enhanced blood flow to hypoxic tubules with newer vasoactive agents, such as those modulating endothelin-mediated vasoconstriction, may also have value in human ARF.

Advances in supportive therapies for dialysis-requiring ARF must focus on clarifying the respective roles of continuous and intermittent treatment modalities. Since outcomes in ESRD are inversely related to the dialysis dose delivered, intensive dialysis needs to be pursued with further evaluation of its role in ARF. It will be necessary to modify quantification techniques of the delivered dialysis dose in ARF to account for the confounding factors posed by the non-steady state metabolic characteristics, variable volumes of solute distribution, and impaired tissue perfusion that exist in this population of patients. Prescriptions may need to be related to urea generation as a marker of catabolic rate, and delivered dose may require dialysate-side quantification of solute clearance [9].

Improvements in dialysis and hemofiltration, however, only replace the filtrate function of the kidneys. Renal tubules also have important reabsorptive, homeostatic, metabolic, and endocrine functions. Replacement of these lost functions through cell therapy or tissue engineering in patients with ATN could be helpful in providing more complete support during the maintenance phase of ATN, and might enhance a speedier recovery and improve overall prognosis. Cell therapy is an evolving strategy that uses cells as vehicles for delivery of drugs by taking advantage of their synthetic and metabolic properties. A “bioartificial” renal-tubule device that uses epithelial progenitor cells is currently being tested in preclinical trials [29]. Its potential additive benefits in treating syndromes of ARF are also worthy of continued investigation, as it provides a unique and novel supportive strategy.

Conclusion

ARF is a serious, common, complicated and costly medical illness. Other comorbid conditions may accompany ARF, often as a presentation of multiple organ dysfunction. Management of these issues is outside the scope of this chapter. The precise contribution of ARF to these other serious comorbid conditions is sometimes difficult to determine. The dictum that people *die with* and not *of* ARF, however, suggests that if only we could manage all the other combined problems better, our current sophistication in terms of renal replacement therapy is good enough to ensure survival. However, it has been suggested that renal failure per se affects mortality rates [36] and that improving biocompatibility of dialysis treatments enhances survival [27]. It is thus more likely that the high mortality rate in ARF is determined by complicated interdependent relationships among all the existing comorbid conditions, including ARF itself.

Much progress needs to be made in both the prevention and treatment of patients with ARF. We believe that interventions which improve the treatment of ARF or shorten its duration will translate into lives saved.

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Clinical Manifestations of Chronic Renal Insufficiency

Paolo Fanti

Introduction

Progression to end-stage renal disease (ESRD) is characterized by the disruption of a number of biological functions, including fluid and electrolyte balance, intermediate metabolism, and endocrine, neurological, hematological, cardiovascular, gastrointestinal, cutaneous and ophthalmologic functions. This brings about a large and characteristic cohort of clinical manifestations that constitute the uremic syndrome. Uremia starts to declare itself to patient and physician when renal function drifts below 30%. However, individual manifestations do not appear simultaneously, but rather depend on the degree of loss of glomerular filtration rate (GFR); on the concomitance or pre-existence of other pathologies such as diabetes mellitus (DM), coronary artery disease (CAD), and peripheral vascular disease (PVD); and on the individual predisposition of a patient. The following review of the clinical manifestations and management of the uremic syndrome is limited to the period preceding the institution of renal replacement therapy (RRT).

Water and Electrolyte Balance

Water Balance

Progressive loss of the structural integrity of the nephrons and anatomical derangement of the renal medulla causes loss of renal responsiveness to anti-diuretic hormone (ADH). This, along with the increased single-nephron GFR and the increased filtered load of solutes such as urea, impairs the renal concentrating and diluting functions. Under these conditions, the urine approaches isosthenuria, i.e. urine osmolality equal to that of serum, and the solute excretion becomes the main determinant of water excretion. The practical consequence of this phenomenon is that patients with advanced renal insufficiency are at risk of developing either dehydration and hypernatremia, or water intoxication and hyponatremia, when water intake is less or more, respectively, than mandated by the solute load.

Sodium (Na^+) Balance

Na^+ load per nephron increases as renal function is progressively lost, and both humoral and renal tubule adaptative mechanisms are activated to decrease tubular Na^+ reabsorption and to maintain Na^+ balance. In

advanced renal insufficiency, excessive Na^+ intake tends to cause Na^+ retention and volume overload because of the preexisting maximal or close-to-maximal depression of renal tubule reabsorption. Conversely, the ability to lower Na^+ excretion during Na^+ restriction is hindered by the increased osmotic diuresis per nephron. Thus, patients with advanced renal insufficiency tend to develop volume overload or volume depletion, respectively, when the dietary Na^+ intake is excessively large or small.

Potassium (K^+) Balance

As is the case with Na^+, the K^+ load per nephron increases in advanced renal failure. Differently from Na^+, however, K^+ balance is maintained primarily by changes in tubular secretion rate. This is accomplished primarily by activation of the renin-angiotensin system and consequent increased distal tubular K^+ excretion. Large intestine excretion of K^+ is also responsive to this hormonal system, and it contributes some to the maintenance of K^+ homeostasis in chronic renal failure (CRF). The importance of the renin-angiotensin-aldosterone axis in the maintenance of K^+ balance is underscored by the observation that CRF patients with anatomic damage of the juxtaglomerular apparatus and with hyporeninemic hypoaldosteronism frequently experience hyperkalemia. Even when this hormonal system is normally functional, patients with CRF usually do not tolerate excessive dietary K^+ intake or the use of β-adrenergic receptor agonists, nonselective beta blockers (which impair K^+ entry into cells), nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and K^+-sparing diuretics (which impair tubular K^+ excretion).

Intermediate Metabolism

Protein Metabolism and Calorie Requirement

The minimum daily protein requirement of moderately active healthy adults in energy balance is commonly set at 0.6 g/kg/day of high biological value proteins. In Western postindustrial societies, the average protein intake is higher than 1 g/kg/day and includes a large proportion of high biological value proteins. Healthy individuals tolerate this excess of proteins relatively well due to biochemical pathways that dispose of surplus amino acids. Conversely, patients with advanced renal insufficiency cope poorly with excessive protein intake. Inability to dispose of the degradation products derived from excess protein intake leads to accumulation of: (1) nitrogen moieties that contribute to uremic symptoms, (2) titratable acid leading to metabolic acidosis, (3) phosphates with secondary hyperparathyroidism, and (4) Na^+ with volume expansion and arterial hypertension. An increased renal load of osmotically active moieties and phosphates is also believed to accelerate the progressive loss of renal function. Additionally, recent observations indicate that unrestricted protein intake is harmful for patients with the nephrotic syndrome, as it seems to worsen these individuals' proteinuria and hypoalbuminemia.

For these reasons, protein-restricted diets have been utilized for > 3 decades in the management of patients with CRF [1, 2]. The soundness and safety of this practice has been corroborated over the years by a large body of clinical observations and experimental studies which show:

– protein-restricted diets do indeed prevent or ameliorate many symptoms and com-

plications of CRF and they might slow the progressive loss of renal function;
- the rates of amino acid metabolism and the energy expenditure of nonacidotic patients with CRF are not different from those of healthy controls, both at rest and during exercise [3, 4]; and
- normal subjects and patients with CRF are equally able to achieve neutral nitrogen balance when fed low amounts of high biological value proteins (0.6 g/kg body weight/day), as long as they are provided with adequate amounts of energy (≥ 35 kcal/kg/day) [5].

Despite these findings, most studies of patients on dialysis indicate that these individuals are malnourished [6, 7] and that malnutrition often antedates the dialysis therapy [8]. This is of major concern since malnutrition at the onset of ESRD is a potent predictor of increased morbidity and mortality, as shown in studies with up to 5 years of follow-up [9, 10]. Protein and/or energy intake below the thresholds given above are important contributing factors [11], because it is known that patients with GFR below 25% tend to suffer from anorexia [12]. In addition, It is believed that accelerated protein catabolism may be as important in promoting malnutrition. Conditions that promote protein degradation during advanced renal insufficiency include
- inadequate energy intake in concomitance with a protein-restricted diet, because patients with CRF are unable to adapt to low protein diets when the caloric intake is < 35 kcal/kg/day;
- metabolic acidosis, which starts to develop with a GFR < 40 mL/min [13];
- depressed anabolic effect of insulin on muscle protein synthesis; and
- chronic inflammatory conditions with increased pro-inflammatory cytokine activity.

Treatment

Protein restriction should be implemented in those patients who are motivated and capable of following the rather stringent rules of this diet. The goals of nutritional therapy are to prescribe a diet sufficient to prevent malnutrition, to diminish the accumulation of nitrogenous waste and metabolic disturbances characteristic of uremia, and to slow the progression of renal failure. Protein intake is determined based on the degree of renal insufficiency, the presence of progressive renal failure, the level of proteinuria, the presence of diabetic nephropathy, and the concomitant use of glucocorticoids.

Lipid Metabolism

Abnormal serum lipid and lipoprotein concentrations are present early in patients with CRF and are only marginally affected by the degree of renal failure and by the use of dialysis. This metabolic abnormality is a likely important contributor to the high incidence of atherosclerosis and cardiovascular disease in the CRF population. Although total cholesterol is frequently normal, the serum concentrations of low-density lipoproteins (LDL) and high-density lipoproteins (HDL) cholesterol tend to be high and low, respectively. Triglyceride levels are often elevated, due to low lipoprotein lipase activity and impaired conversion of very-low density lipoproteins (VLDL) to LDL. Low activities of lipoprotein lipase, hepatic triglyceride lipase and lecithin cholesterol acyltransferase result in accumulation of intermediate density lipoproteins (IDL) and reduction of HDL. Factors such as insulin resistance or deficiency, hyperparathyroidism, carnitine deficiency, and altered

lipoprotein content of the VLDLs have been proposed as contributors to the decreased lipase activity. Recently, several groups have reported the frequent occurrence of high levels of lipoprotein(a) (Lp(a)) and of oxidized lipid moieties in the circulation of patients with ESRD [14 – 16] and CRF [17]. The observation that both Lp(a) and oxidized lipids contribute to cardiovascular disease in subjects with normal renal function justifies the recent interest in the possible role of these factors in the progression of atherosclerosis in renal patients. Interestingly, high blood levels of both Lp(a) and oxidized lipids are favored by increased oxidative stress and chronic inflammation, conditions that frequently occur in CRF patients.

Treatment

Because accelerated atherosclerosis and cardiovascular disease are the leading cause of morbidity and mortality in patients with CRF, prophylactic treatment of these conditions should be considered in patients with chronic renal insufficiency. Unfortunately, very limited information is currently available on the effectiveness of long-term lipid reduction therapy in this patient population, and most of the practices in this area are based on clinical trials in populations without renal disease. In general, these patients should be instructed to follow the American Heart Association step 1 diet, which provides < 30% of total calories from fat and < 10% of total calories from saturated fat. Also, all patients are urged to achieve desirable body weight and to maintain cardiovascular fitness with daily exercise. Pharmacological intervention with β-hydroxy-β-methyl glutaryl coenzyme A (HMG-CoA) has been proposed for individuals with LDL persistently > 140 mg/dL [18]. Gemfibrozil can also be used with pronounced lowering effects on the triglycerides and some modest effect on LDLs [19]. The practice of prescribing antioxidants such as high dose α-tochopherol is gaining popularity to reduce oxidative stress and ameliorate the chronic inflammation seen in these patients. However, high-dose ascorbic acid (vitamin C) should be avoided because of the tendency of this moiety to be converted to oxalic acid, resulting in oxalosis.

Carbohydrate Metabolism

Moderate and advanced renal insufficiency is associated with glucose intolerance, caused in part by acquired resistance of the target organs to the insulin action. In these patients, normal binding of insulin to its receptor is not followed by adequate activation of the postreceptor pathways that mediate this hormone's cellular actions. An additional cause of glucose intolerance in renal insufficiency is the abnormal pancreatic release of insulin in response to glucose. Secondary hyperparathyroidism contributes to the latter abnormality because PTH increases intracellular levels of calcium. These metabolic aberrances may require the institution of exogenous insulin therapy in patients with noninsulin-dependent (Type II) DM who develop moderate renal insufficiency. Paradoxically, the insulin requirement of diabetics with renal insufficiency tends to decrease as the renal function falls below 20%, due to reduced renal degradation of proinsulin, C-peptide, and both endogenous and exogenous insulin, resulting in higher blood levels of these peptides.

Immunity, Inflammation and Oxidative Stress

Both humoral [20, 21] and cellular immunity [22] are compromised as renal function is progressively lost [23]. This acquired immunodeficiency state contributes to increased infection risk [24], anergy, poor response to vaccines, and decreased autoimmune disease activity. Paradoxically, this immunodeficiency state is associated with sustained activation of several cell types that participate in the host defense, including the monocytic cell line [25]. Activated monocytes and macrophages are integral elements of the smoldering multifactorial inflammatory state that is often detected in renal failure patients. This develops early in the course of renal failure and is characterized by the presence of high circulating levels of C-reactive protein (CRP) [26, 27], lipopolysaccharide binding protein [28], interleukins IL-1β and IL-6, and tumor necrosis factor-α (TNF) [29, 30], as well as the presence of cytokine-specific inhibitors, including interleukin-1 receptor antagonist (IL-1Ra) and tumor necrosis factor soluble receptors (TNFsRs) [31]. This chronic inflammatory state is intimately linked to increased monocytic and neutrophilic production of reactive oxygen species. Since both exogenous and endogenous antioxidants such as α-tocopherol [32, 33], ascorbic acid [34], superoxide dismutase [35], and the glutathion system [36] are decreased in CRF, the high production of reactive oxygen species results in oxidative damage and further stimulates inflammation [37 – 39]. Indeed, markers of lipid and protein oxidation are elevated in advanced chronic renal insufficiency [40 – 42]. During the last decade, evidence has accumulated to suggest that inflammation and oxidative stress contribute substantially to the high morbidity and mortality of renal failure patients by promoting anorexia, wasting, malnutrition [43, 44], accelerated atherosclerosis [45] and premature cardiovascular disease [46].

Treatment

Prospective studies demonstrating the safety, efficacy, and cost effectiveness of measures aimed at identifying and treating inflammation and oxidative stress in the renal failure population are lacking. Based on the currently available evidence, the measurement of CRP seems a reasonable test to survey patients with chronic renal disease for signs of chronic inflammation and oxidative stress. High levels should prompt a search for potentially correctable causes, such as infections, drug allergies, autoimmune disease, and cancer. Also, a therapeutic trial with antioxidants may be considered. Alpha-tocopherol is a good candidate since it is a potent dietary antioxidant, its level is low in renal failure patients, and it does not present any specific toxicity for the renal failure population. Ascorbic acid has a synergistic effect with α-tocopherol in its antioxidant activity. However, prudence should be exercised, since it is converted to oxalic acid and may cause oxalosis.

Endocrine Systems

Divalent Ion, Parathyroid Hormone (PTH) and Vitamin D Metabolism

Early signs of altered mineral homeostasis can be detected in most patients with 50% reduction of GFR, although the laboratory

and clinical signs become obvious in all patients when the GFR is < 25 – 30%. During progressive loss of renal mass, the remaining functional tissue adapts by decreasing tubular reabsorption of ultrafiltered phosphorus (Pi), leading to increased single-nephron excretion of this ion. In advanced renal failure, the fractional excretion (FE) of Pi can be as high as 90% [47, 48]. This compensatory mechanism allows maintenance of adequate renal Pi clearance until the GFR is < 20 – 25 mL/min, at which point the residual renal mass is often unable to handle the normal dietary intake of Pi and hyperphosphatemia develops. Serum calcium (Ca) declines progressively in moderate and advanced renal insufficiency, due in part to the formation of Ca-Pi products (see above), but mostly because of progressive development of calcitriol deficiency and of target-organ resistance to this hormone, leading to inadequate intestinal absorption of Ca. The calcitriol deficiency is caused primarily by the progressive loss of renal mass, which is essential for the production of calcitriol, and also by the inhibitory effect of hyperphosphatemia on the renal production of this hormone. Hyperphosphatemia, hypocalcemia and calcitriol deficiency are stimuli to the production of PTH, and they all contribute to the development of secondary hyperparathyroidism. The clinical consequences of these divalent ion and hormonal abnormalities are secondary hyperparathyroidism, renal osteodystrophy, and soft tissue calcifications [49]. Hypocalcemia develops slowly and it becomes symptomatic (muscle twitching or frank tetany) almost exclusively associated with an abrupt rise of systemic pH, which in turn causes a fall in ionized Ca. Soft tissue calcifications usually occur when the Ca-Pi product (both expressed in mg/dL) exceeds 70 and they affect primarily the blood vessels, skin, cornea, and periarticular tissues. Pseudo/gout, i.e. intraarticular deposition of Ca pyrophosphate crystals, with clinical manifestations indistinguishable from those of gout, can occur in patients with advanced renal insufficiency. High blood levels of PTH and skin deposition of Ca-Pi products are important contributors to the development of pruritus. Prior to the diagnosis of ESRD, renal osteodystrophy is most often asymptomatic, although the most severe cases of secondary hyperparathyroidism are associated with early onset of bone pain and skeletal deformities. Additionally, patients with severe secondary hyperparathyroidism have a high rate of bone turnover with excess release of Pi from bone, which can contribute substantially to the maintenance of hyperphosphatemia.

Treatment

In patients with moderate to severe renal insufficiency, serum Pi should be maintained at 4.0 – 5.5 mg/dL. Reductions of Pi intake to 10 mg/kg/day, which is implemented primarily to slow the progression of the renal failure, contribute to the control of hyperphosphatemia. Small amounts of Pi binders are often required once the GFR is below 25%. Ca acetate and Ca carbonate are the most popular choices [50]; aluminum-containing Pi binders should be avoided even at this stage of renal disease. Organic polymer-based phosphate binders have been tested successfully, and they were recently introduced to the market [51]. Serum Ca levels should be maintained in the normal range. Intake of Ca-containing Pi binders with meals inevitably results in intestinal absorption of small amounts of Ca. Serum Ca levels > 10.0 mg/dL should be avoided to prevent further deterioration of renal function. When serum Ca is low and Pi is normal, Ca salts can be given between meals to increase Ca absorption without interfering with the absorption of dietary Pi. Cir-

culating intact PTH should be checked once yearly to rule out the presence of advanced secondary hyperparathyroidism. If PTH is > 3-fold above the upper limit of normal, therapy with calcitriol should be started at the low dose of 0.125 μg/day. This calcitriol dose is effective at reducing circulating PTH without causing deleterious effects such as hypercalciuria, hypercalcemia or loss of renal function [52, 53]. Hypercalcemia is a rare event in the predialysis population, and it should be avoided to prevent further renal damage.

Reproductive System

Dysfunction of the hypothalamic-pituitary-gonadal axis becomes clinically apparent with a GFR < 20 mL/min. Men and women are affected alike, although the deficiency is more obvious in men. In both genders, sexual desire and activity are inversely proportional to the severity of uremia [54]. Indifference to sexual activity can develop with advanced renal failure. In women, menstrual irregularities consistently follow the deterioration of the renal function. Oligomenorrhea occurs with GFR < 15 ml/min and amenorrhea occurs once the GFR is below 5 ml/min. In men, decreased libido and performance develop as the renal function deteriorates and impotence is present in as many as 56% of men with ESRD [55]. The testicles are soft and atrophic, and spermatogenesis is impaired or absent. Gynecomastia occurs more often after dialysis is started. Adolescents suffer from delayed puberty with retardation of skeletal growth. The pathogenesis of these abnormalities seems to be related to direct or indirect effects of uremia on both the hypothalamic-pituitary system and on the gonads. The roles of anemia, zinc deficiency and secondary hyperparathyroidism have been reported. Relatively frequent issues that come up in young women with renal disease are the counseling and management of pregnancy. Pregnancy outcome is 90% successful in women with a serum creatinine < 1.5 mg/dL [56, 57]. When the serum creatinine is > 1.5 mg/dL, the therapeutic abortion rate is 13 – 24% [58, 59], and 56 – 63% of deliveries are preterm, mostly due to worsening renal function, hypertension, abruptio placentae, and fetal distress [60, 61]. Fetal survival ranges from 60 – 92% with highest frequencies in the most recent reports [62]. The presence of maternal hypertension seems to substantially affect the fetal outcome, since preterm birth and growth retardation are more common in hypertensive than normotensive women [63]. Recent progress in medical and pharmacologic management of mother and fetus may continue to improve the fetal outcome in women with chronic renal insufficiency and hypertension.

Growth Hormone System

Growth hormone and the radioimmunoassayable levels of the insulin-like growth factors (IGFs) are elevated in renal failure. However, the bioassayable levels of the IGFs are low due to the presence in the uremic serum of low-molecular-weight inhibitors of the IGFs. This accounts for the stunted growth of children with renal insufficiency, which responds favorably to exogenous administration of recombinant human growth hormone.

Thyroid Hormone

Total thyroxine (T4), free thyroxine index (FTI), total triiodothyronine (T3) and free triiodothyronine index tend to be low in renal

failure while the reverse T3 level is normal. Despite these hormonal abnormalities, the thyroid-stimulating hormone (TSH) and the basal metabolic rate are normal.

Hematology

Hematopoietic System

The hemoglobin concentration in azotemia has roughly the same prognostic significance as the creatinine level [64]. In over 90% of the patients with CRF, the hematocrit (HCT) starts to fall when the creatinine clearance reaches 30 – 35 mL/min. Exceptions are patients with polycystic kidney disease (PKD), acquired multicystic disease, hypertensive nephrosclerosis, and some diabetics who can maintain normal HCTs well into end-stage renal disease (ESRD). The anemia is usually normochromic and normocytic. The most important factor by far in the development of anemia is the decreased production of erythropoietin, which normally regulates the bone marrow erythrocyte production. Other factors include:

- resistance to erythropoietin due to deficiency of iron or folic acid; reticuloendothelial blockade from infections, cancer and inflammatory states [65 – 68]; myelofibrosis; aluminum intoxication [69]; bone marrow fibrosis secondary to severe hyperparathyroidism [70, 71];
- shortened erythrocyte life span [72] and possibly neocytolysis [73]; and
- occult bleeding.

Anemia has a profound effect on these patients' general well being and on the performance of their cardiovascular and central nervous systems. Anemia results in progressive reduction of activity and energy level and of exercise tolerance [74]. This is associated with left ventricular dilatation and diastolic dysfunction [75]. Additionally, anemia causes deterioration of the cognitive function and contributes to the neurobehavioral syndrome of uremia that is characterized by confusion, inability to concentrate, decreased mental alertness and impaired memory [76, 77]. The association between anemia, intractable pruritus, and high circulating histamine concentration was reported in a subset of CRF patients [78]. Anemia has also been implicated in the impairment of sexual function that is common in patients with CRF [79].

Treatment

The mainstay of anemia management is the systemic administration of recombinant human erythropoietin (rHu-Epo) with concomitant adequate support of iron stores. RHu-Epo is started when the HCT drops below 30%. A starting dose of 100 – 150 U/kg 3 times/week achieves HCTs > 35% within 4 weeks. The dose is subsequently adjusted to approximately 25 U/kg once weekly, based on individual response [80]. Initiation of rHu-Epo therapy must be preceded by assessment of iron stores. Iron should be replaced to maintain the transferrin saturation > 16% and ferritin > 80 µg/L. In resistant cases, occult blood loss, hemolysis, inflammation, infection, malignancy, aluminum toxicity, vitamin B12 and folate deficiency, myelofibrosis, red cell enzyme defect and hemoglobinopathies should be considered and corrected [81]. Nephrectomy of failed allografts, empiric treatment with broad spectrum antibiotics, and a cycle of steroids may be considered [82].

Coagulation System

The bleeding tendency is characterized by prolonged bleeding time, and it is rarely of clinical consequence before the GFR falls below 15%. The pathogenesis relates to dysfunction of platelet aggregability, but also to abnormal function of the vascular endothelial wall, to aberrant interaction of platelets and endothelium and to the anemia. Treatment of the bleeding diathesis is required before surgical procedures and during active bleeding. Correction of concomitant anemia with transfusions or rHu-EPO injections are often effective at shortening the bleeding time. 1-deamino-8-D-arginine (DDAVP), either 0.3 μg/kg intravenously (IV) or 3 mg/kg intranasally, restores hemostasis within 30 – 120 minutes and for as long as 8 hours, although repeated administration quickly results in tachyphylaxis. Transfusions of cryoprecipitate are effective for 12 – 18 hours from the time of infusion, but they carry a risk of transmitting viral infections. Conjugated estrogens (0.6 mg/kg/day for 5 days) correct hemostasis one day after administration and last for up to 2 weeks.

Cardiovascular System

Systemic Hypertension

Hypertension is the initial cause of renal disease in approximately 3% of Caucasians and 16% of African-Americans with CRF [83]. Conversely, hypertension develops in virtually all cases of CRF secondary to glomerular and renal small vessel disease, and in 40 – 70% of the cases secondary to tubulointerstitial disease. Hypertension is one of the earliest manifestations of chronic renal insufficiency, since it is diagnosed even with minimal loss of renal function and can precede the onset of most signs and symptoms of uremia by many years. Hypertension of renal disease accelerates the progression of the already present renal damage and the development of congestive heart failure (CHF), CAD, and cerebrovascular disease. The major factors involved in the pathogenesis and maintenance of hypertension in CRF are salt and water retention, enhanced activity of the renin-angiotensin system, and increased sympathetic tone. Other possible contributors are the decreased production of the endothelium-relaxing factor nitric oxide and the presence in the circulation of inhibitors of the Na-K-ATPase pump.

Treatment

Treatment of hypertension is essential in CRF, because it slows down the progression of the renal damage and decreases morbidity and mortality. The definition of satisfactory blood pressure control in renal failure is not well established, although the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) recommends controlling the blood pressure to 130/85 mmHg (mean arterial pressure (MAP) 100 mmHg) in individuals without proteinuria and to 125/75 (MAP 92 mmHg) in individuals with > 1 g/day of proteinuria [84]. The management of the hypertension of CRF presents 3 major challenges:

- hypertension is often severe and difficult to control, thus requiring the use of ≥ 2 medications;
- the choice of the antihypertensive agents must take into account the coexistence of several medical conditions that can be

exacerbated by antihypertensive therapy, including DM, dyslipidemias, LVH, and accelerated atherosclerosis; and

– the pharmacology of many antihypertensive agents is altered in renal failure, often leading to special posology requirements, to altered type and frequency of side effects as compared to the normal renal function population, and in some instances to outright contraindication of their use.

Nonpharmacologic intervention should include restriction of sodium chloride intake to < 6 g/day (100 mmol of elemental Na^+), daily moderate exercise, and weight reduction. Pharmacologic intervention often starts with a diuretic which, for GFR < 50%, should always be a loop diuretic. For these levels of compromise in renal function, the thiazides should be used only as an adjunct to loop diuretics in the rare cases of resistance to loop diuretics. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blockers have been shown to have renal protective effects. When tolerated, they can be either added to the diuretic or used as first-line agent. When ACE inhibitors and Ang II receptor blockers are not tolerated, the calcium channel blockers are a good alternative. The nondihydropyridine calcium channel blockers (verapamil and diltiazem) seem to have renal protective effects of somewhat lesser magnitude than the ACE inhibitors, although not all studies have reported this effect. Conversely, the dihydropyridine calcium channel blockers (nifedipine, amlodipine, felodipine, isradipine, and nicardipine) appear to be neutral in terms of renal-protective effects. Beta-blockers are a good alternative to ACE inhibitors, Ang II receptor blockers, and calcium channel blockers. The selection of a beta-blocker should try to match the pharmacologic features of the individual drug with each patient's special needs. Beta-blockers with intrinsic sympathetic activity (Table 1) can be prescribed in the attempt to minimize unwanted effects on lipid metabolism and exercise tolerance. Beta-blockers with poor lipid solubility can be chosen to minimize diffusion in the nervous system and the occurrence of central nervous system (CNS) side effects. β_1-selective blockers should be prescribed when the presence of CAD is documented or strongly suspected. Beta-blockers with extensive hepatic elimination can be used when toxicity due to excess accumulation is a concern. Central alpha agonists (clonidine) and peripheral alpha-adrenergic receptor blockers (terazosin and doxazosin) are effective third-choice antihypertensives. Minoxidil and hydralazine are potent peripheral vasodilators that are often effective in cases of tenaciously resistant hypertension.

Cardiac Function

Congestive heart failure (CHF) is often present in patients with advanced renal insufficiency. Ischemic heart disease, hypertrophic and/or dilated cardiomyopathy are frequently present and should be managed with the same diagnostic and therapeutic principles that apply to cardiac patients with normal renal function. Manifestations of CRF that often participate in the development and/or exacerbation of CHF are hypertension, anemia, fluid overload, and electrolyte abnormalities including hyperkalemia, hypocalcemia, and acidosis. These should be carefully looked for and aggressively treated and prevented. Uremia per se is believed to affect myocardial contractility, the most convincing evidence coming from the incidental observation of improved cardiac function after renal transplantation and from animal studies [85]. Disturbances of

Table 1. Pharmacological Properties of Beta-blockers. Modified from [88]

Drug	Trade name	β_1-Selectivity	Intrinsic Symp. Activity	d Blockade	Lipid Solubility	Renal Elimination	Dose
Acebutolol	Sectral	+	+	–	++	0	200 – 800 qd
Atenolol	Tenormin	++	–	–	–	100	12.5 – 25 qd
Betaxolol	Kerlone	++	0	–	–	0	5 – 20 qd
Bisoprolol	Zebeta	++	0	–	++	50	2.5 – 5 qd
Carteolol	Cartrol	0	+	–	–	100	1.25 – 2.5 qd
Carvedilol	Coreg	–	0	+	++	10	12.5 – 50 bid
Celiprolol	Selectol	++	+	–	–	50	200 – 400 qd
Labetalol	Normodyne	–	+	+	+++	60	200 – 1200 bid
Metoprolol	Lopressor	++	–	–	+++	0	50 – 200 bid
Nadolol	Corgard	–	–	–	–	100	40 – 320 qd
Penbutolol	Levatol	–	+	–	+++	0	10 – 20 qd
Pidolol	Visken	–	+++	–	++	40	10 – 60 qd
Propranolol	Inderal LA	–	–	–	+++	0	40 – 480 qd
Timolol	Blocadern	–	–	–	–	20	20 – 60 bid

qd = daily, bid= twice daily

the cardiac rhythm are relatively frequent in renal insufficiency and are mostly related to electrolyte imbalance (hyperkalemia, hypermagnesemia, hypocalcemia, acidosis) or to drug toxicity (digoxin, procainamide, renally-excreted β-blockers). Pericarditis used to occur in about half of the patients who died from uremia before the advent of dialysis. Currently, this condition is much less frequent and is almost always detected once ESRD is reached. Uremic pericarditis in advanced renal insufficiency is a fibrinous inflammatory process. Onset of pericarditis is in itself an indication for initiation of chronic RRT.

Neurologic System

Peripheral Neuropathy

Peripheral neuropathy develops early in chronic renal insufficiency, and abnormalities of the nerve conduction velocity test are often detected much earlier than the onset of symptoms. The onset of symptoms is insidious but very frequently present once the GFR is < 30 mL/min. Peripheral neuropathy is symmetrical, insidious in onset, and slowly progressive. It begins distally and spreads proximally, with the lower extremities being affected first. It is sensorimotor, with the sensory involvement preceding the motor involvement. It is indistinguishable from diabetic neuropathy

and the 2 very often overlap. Loss of 2-point discrimination, vibratory perception, and paresthesias are common. When the GFR is < 15 mL/min, the restless-leg syndrome can occur, with sensations of crawling, prickling and pruritus that worsen with rest and in the evening and improve with movement. The burning-feet syndrome is less frequent and characterized by tenderness and sensation of swelling of the lower extremities. The motor deficit occurs later and is characterized by loss of deep tendon reflexes, weakness of dorsiflexion of the feet, limb weakness, and unsteady gait. The neurological deficit is only partially reversed by RRT, with Wallerian degeneration and neuron loss accounting for the irreversible component of the syndrome. Presence of severe peripheral neuropathy is an indication for initiation of RRT, since procrastination can result in irreversible damage. Low dose tricyclics (e.g. amytriptiline) are moderately effective. The author has had favorable anecdotal experience prescribing the anticonvulsant gabapentin for treatment of symptoms related to peripheral neuropathy [86, 87].

Autonomic Dysfunction

The most frequent and troublesome manifestation is gastroparesis, which overlaps with diabetic gastroparesis. Other manifestations are orthostatic hypotension, impaired sweating and abnormal response to the Valsalva maneuver.

Uremic Encephalopathy

Patients with GFR < 20 mL/min can develop symptoms of reduced general cerebral activity with disturbances of mentation and cognition. These symptoms are more frequent and pronounced in the elderly, especially if uremia is superimposed on preexisting organic damage of the brain. Frequent initial symptoms are apathy, fatigue, confusion, narrowed attention span, impaired memory, and somnolence. The normal sleep pattern is often affected with altered day-night rhythm. More advanced symptoms, that usually occur with GFR < 10 mL/min, are disorientation, irritability, inappropriate behavior, hallucinations, delusion, anxiety, lethargy, stupor, and coma. The latter more advanced symptoms are almost never experienced nowadays, because of intervention with RRT.

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Drug Dosing in Renal Failure

George R. Aronoff

Introduction

Uremia affects every organ system in the body. Since the kidney is the major regulator of the internal fluid environment, the physiological changes associated with renal disease have pronounced effects on the pharmacology of many drugs. Clinicians must consider changes in the absorption, distribution, metabolism, and excretion of drugs and their active or toxic metabolites when treating patients with impaired renal function. Renal diseases are often superimposed on underlying problems, such as hypertension, diabetes mellitus (DM), and heart disease. These co-morbidities compound the complexity of management.

The number of patients with impaired renal function has increased. Improvements in the management of patients with chronic diseases that decrease renal function have expanded the numbers of patients with impaired renal function, because they live longer. Advanced age, DM, and coronary artery disease (CAD) are no longer barriers to chronic renal replacement strategies. In addition, renal function decreases with age, and older patients make up the most rapidly growing patient group for which special understanding of drug disposition is important.

New dialysis membranes and devices, acceptance of intermittent and continuous peritoneal dialysis, and the application of continuous extracorporeal renal replacement therapies (RRT) contribute to the need for detailed understanding of drug transport across biological and artificial membranes. Physicians caring for these patients must understand the biochemical and physiologic effects of uremia on drug disposition and the effects of dialysis on drug and metabolite removal. This chapter provides a rational schema of pharmacotherapy for patients with decreased renal function and for those on dialysis.

Patient Assessment

Appropriate pharmacotherapy for patients with kidney disease begins with a careful history and physical examination. Previous medications, concurrent medicines, and drug-related allergy or toxicity are important in the initial evaluation of patients with impaired renal function. Preventing potential drug interactions before choosing a drug regimen reduces adverse drug effects. For example, dialysis patients average > 8 concurrent medications and suffer 3 times the incidence of adverse drug events as patients with normal renal function [1, 2].

Establishing specific diagnoses before initiating drug therapy permits clinicians to avoid polypharmacy and decreases the chances of untoward drug interactions. Individualizing therapy allows one drug to treat several con-

ditions. For example, an angiotensin converting enzyme (ACE) inhibitor used to lower blood pressure in a hypertensive patient can also improve heart failure and slow the progression of diabetic glomerulosclerosis.

The extracellular fluid volume determines the distribution volume of many drugs. Edema or ascites increases the volume of distribution of water-soluble drugs, while dehydration contracts this volume. Determination of an appropriate loading dose requires an assessment of hydration status.

Similarly, accurate drug dosing requires measurements of body height and weight. Ideal body weight (IBW) can be a guide for dosing obese patients. For men, IBW is 50 kg plus 2.3 kg for each inch (2.54 cm) over 5 feet (152 cm). For women, IBW is 45.5 kg plus 2.3 kg for each inch (2.54 cm) over 5 feet (152 cm). Many clinicians use the average of the measured body weight and the ideal body weight as the value on which to base drug doses [3].

Functional impairment of other excretory organs influences drug therapy in patients with renal disease by limiting alternative pathways for drug and metabolite elimination. Finding the stigmata of liver disease is a strong indication of the need to further decrease drug doses in patients with renal impairment.

Measurement of Renal Function

The rate and extent of drug and metabolite elimination by the kidneys is proportional to the glomerular filtration rate (GFR). Although the serum creatinine measurement is frequently used to establish renal function, this measurement also reflects muscle mass. Serum creatinine measurements within the normal range will not accurately estimate renal function in elderly or debilitated patients. In such patients, the use of standard drug doses may result in serious overdose and toxic drug or metabolite accumulation.

The Cockroft and Gault equation, shown below, relates the serum creatinine measurement to the patients age, body mass, and gender.

$$C_{cr} = \frac{(140 - age) \times (IBW)}{72 \times S_{cr}} \times (0.85 \text{if female})$$

C_{cr} = Creatinine Clearance (mL/min)
S_{cr} = Serum Creatinine (mg/dL)

For obese men and women the equation should be modified:

$$C_{cr}(\text{obesemen}) = \frac{(137 - age) \times \left[(0.285 \times wt) + (12.1 \times ht^2)\right]}{51 \times S_{cr}}$$

$$C_{cr}(\text{obesewomen}) = \frac{(146 - age) \times \left[(0.287 \times wt) + (9.74 \times ht^2)\right]}{60 \times S_{cr}}$$

wt = patient's weight in kg
ht = patient's height in cm

When renal function is unstable, the serum creatinine does not reflect the clearance rate. A timed urine collection, using the midpoint serum creatinine measurement, estimates renal function when the serum creatinine is changing. Oliguric patients usually have a creatinine clearance < 5 mL/min.

Dialysis patients may have residual renal function that contributes to the elimination of drugs and their metabolites. Residual renal function decreases over time but depends on the level of renal function present at the initiation of RRT and the underlying renal disease.

Serum creatinine measurements alone should not be used to estimate intrinsic renal function in dialysis patients. Estimating residual renal function in nonoliguric dialysis patients is difficult, because the serum creatinine reflects the adequacy of dialysis and muscle mass, as well as residual glomerular filtration. Since creatinine clearance measurements do not accurately estimate the GFR in patients with renal failure requiring dialysis, the determination of renal function requires measurement of the plasma clearance rate of radioisotopes.

Medications may interfere with laboratory measurements of renal function. Drugs can falsely increase or decrease the measurement of serum creatinine concentration, urea nitrogen (BUN), and uric acid, and alter urine color or urine protein concentration.

Effects of Uremia on Drug Disposition

Bioavailability

Drug bioavailability is the amount of a drug that enters the central circulation and the rate at which it appears in the blood. Intravenous (IV) drugs enter the central circulation directly. They have a rapid onset of action. Other routes of administration require that the drugs cross a series of biological membranes and pass through organs that may eliminate some of the drug before it reaches the site of action. Only a fraction of the dose reaches the systemic circulation. The measurement of bioavailability is expressed as the percentage of the dose that reaches the systemic venous circulation. The time required to achieve the maximum concentration of the drug in venous blood reflects the rate of drug absorption.

The rate and extent of gastrointestinal (GI) absorption are important considerations for oral drugs. GI membranes act as a barrier to drug absorption, and the presence of metabolizing enzymes in GI epithelium decreases drug absorption.

Orally administered drugs are first absorbed into the portal circulation. Since these drugs first pass through the liver, bioavailability depends on the extent of hepatic metabolism.

Uremia decreases GI drug absorption. Nausea, vomiting, and gastroparesis are common in uremia, but little specific information about bowel function is available in patients with renal failure. Salivary urea concentrations increase when urea accumulates in the plasma. Gastric urease forms ammonia from swallowed urea. The ammonia buffers gastric acid in uremic patients. The liver regenerates urea from the reabsorbed ammonia as it passes through the portal circulation. This urea-ammonia cycle increases gastric pH and decreases the absorption of drugs that need acid hydrolysis for absorption [4].

Ferrous iron salts require hydrolysis to their ferric form by gastric acid for absorption and are not well absorbed by dialysis patients because of impaired acid hydrolysis in the stomach. In addition, the dissolution of many tablet dosage forms requires the acid environment normally found in the stomach. Absorption of these products is incomplete and occurs more slowly in an alkaline environment.

Patients with renal impairment often ingest large quantities of antacids to bind dietary phosphate. Chelation and the formation of nonabsorbable complexes with multivalent cations frequently used in antacids decrease the bioavailability of some drugs [5]. This effect is particularly important on the absorption of some antibiotics and digoxin.

Craig and colleagues demonstrated impaired GI absorptive function in patients with impaired renal function. They showed that the

absorption of the simple sugar d-xylose is reduced in patients with renal failure [6]. Gastroparesis, commonly observed in diabetic patients with renal failure, prolongs gastric emptying and delays drug absorption. Similarly, diarrhea decreases gut transit time and diminishes drug absorption by the small bowel.

The complex interaction of absorption and first-pass hepatic metabolism causes variable drug bioavailability in patients with renal impairment. For some drugs, decreased biotransformation leads to the appearance of increased amounts of active drug in the systemic circulation and enhanced bioavailability. Conversely, impaired protein binding allows more free drug to be available at the site of hepatic metabolism, thereby increasing the amount of drug removed during the hepatic first pass.

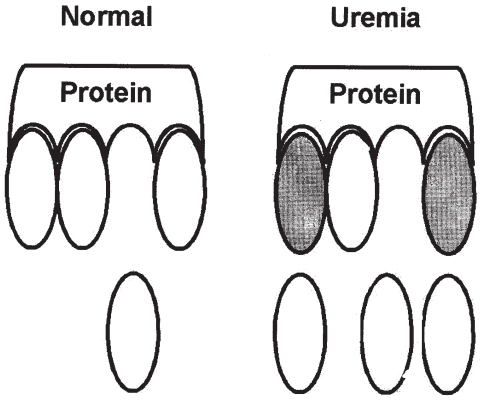

Figure 1. Protein binding defect in uremia. Displacement of drug from its binding site by the accumulation of undefined uremic toxin or a uremia-induced conformational change in the binding site geometry results in more free drug in plasma.

Distribution

Drugs disperse throughout the body at a given rate. At equilibrium, the apparent volume of distribution is the amount of the drug in the body divided by its plasma concentration. This apparent volume of distribution is a mathematical construct used to estimate the dose of a drug to be given in order to achieve a therapeutic plasma concentration rather than an actual anatomical space. Highly protein-bound drugs, or those that are water soluble, are restricted to the extracellular fluid space and have small distribution volumes. Lipid-soluble drugs penetrate body tissues and exhibit large volumes of distribution.

Renal insufficiency frequently alters drug distribution volume. Edema and ascites increase the apparent volume of distribution of highly water-soluble or protein-bound drugs. Usual doses of such drugs given to edematous patients result in lower plasma levels. Conversely, dehydration or muscle wasting decreases the volume of distribution. In these cases, usual doses result in higher plasma concentrations.

Drug binding to plasma proteins influences the volume of distribution, the quantity of free drug available for action, and the degree to which the agent can be eliminated by hepatic or renal excretion. Protein-bound drugs attach reversibly either to albumin or glycoprotein in plasma. Decreased plasma protein binding in patients with renal insufficiency increases drug action, but may also increase the rate of drug removal [7].

A protein-bound drug is in equilibrium with free drug in plasma. As illustrated in Figure 1, a combination of decreased serum albumin concentration and a reduction in albumin affinity for the drug decreases the protein binding of many drugs and shifts the equilibrium to free drug in uremic patients [8]. Even when the plasma albumin concentration is normal, the protein binding defect of some drugs correlates with the level of azotemia [9, 10].

The clinical consequences of impaired plasma protein binding in uremia are impor-

tant. Serious toxicity occurs when the total plasma concentration of a protein-bound drug is pushed into the therapeutic range by increasing the dose. If a significant protein binding defect is present, the concentration of free drug may be toxic. For such drugs, total and unbound plasma concentrations should be measured.

Predicting the clinical effects of altered protein binding in uremia is difficult. Although decreased binding results in more free drug at the site of drug action or toxicity, the distribution volume is increased resulting in lower plasma concentrations. In addition, more unbound drug is available for metabolism and excretion and decreases the half-life ($t^{1/2}$) of the drug in the body.

Metabolism

Renal failure alters drug biotransformation. Uremia slows the rate of reduction and hydrolysis reactions. Glucuronidation, sulfate conjugation, and microsomal oxidation occur at normal rates [11, 12].

The production of active or toxic metabolites is important in patients with renal failure. Metabolites frequently depend on the kidneys for their elimination from the body. Metabolite accumulation explains, in part, the high incidence of adverse drug reactions seen in renal failure.

Drug dosing recommendations for dialysis patients are usually derived from studies in patients with stable, chronic renal failure (CRF) and extrapolated to seriously ill patients with acutely decreased renal function. Acute renal failure (ARF) may spare metabolic drug clearance [12]. Drug dosing schemes extrapolated from individuals with stable CRF could result in potentially ineffectively low drug concentrations in patients with acute renal dysfunction.

Drug Dosing Calculations

When the physical examination suggests that a patient with renal impairment has a normal extracellular fluid volume, an initial drug dose equal to the dose given to a patient with normal renal function should produce therapeutic drug concentrations rapidly. A loading dose of any drug can be calculated from the following expression:

$$\text{Loading Dose} = V_d \times \text{IBW} \times Cp$$

where V_d is the drugs volume of distribution in L/kg, IBW is the patient's ideal body weight in kg, and *Cp* is the desired steady state plasma drug concentration.

For subsequent drug doses, the fraction of the normal dose recommended for a patient with renal failure can be calculated as follows:

$$Df = t½ \text{ normal} / t½ \text{ renal failure}$$

where Df is the fraction of the normal dose to be given; t½ normal is the elimination half-life of the drug in a patient with normal renal function; and t½ renal failure is the elimination half-life of the drug in a patient with renal failure. To maintain the normal dose interval in patients with renal impairment, the amount of each dose, following the loading dose, can be determined from the following relationship:

$$\text{Dose in Renal Impairment} = \text{Normal Dose} \times Df$$

The resulting dose is usually given at the same dose interval as that for patients with normal renal function. This method is effective for drugs with a narrow therapeutic range and a short plasma t1/2. Figure 2 illustrates plasma concentrations following an initial loading dose and reduction of the individual doses.

Prolonging the dose interval in dialysis patients is a convenient method to reduce drug

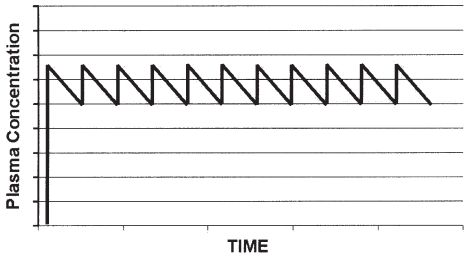

Figure 2. Plasma concentrations following a normal loading dose and reduced maintenance doses. This approach avoids high peak and low trough concentrations and is best for drugs with a narrow range between the therapeutic and toxic concentrations.

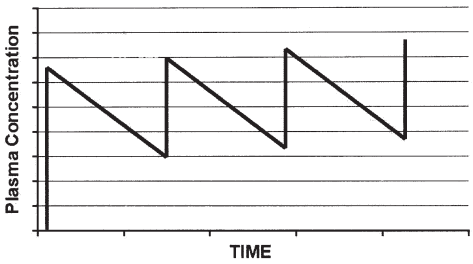

Figure 3. Plasma concentrations following a normal loading dose and repeated normal doses at a prolonged dose interval. Higher peak and lower trough concentrations result.

dosage. This method is particularly useful for drugs with a broad therapeutic range and long plasma $t^{1/2}$. If prolonging the dose interval, rather than decreasing the individual doses, is desirable, the dose interval in renal impairment can be estimated from the following expression:

Dose Interval in Renal Impairment = Normal Dose Interval / Df

If the range between therapeutic and toxic levels is too narrow, either potentially toxic or subtherapeutic plasma concentrations result. The resulting plasma concentrations from prolonging the dose interval in an individual with impaired renal function are shown in Figure 3.

Combining dose reduction and interval prolongation is a practical and convenient approach. The dosage is modified by multiplying the usual daily maintenance dose by the dose fraction. Once the average daily dose is calculated, it can be divided into convenient dosing intervals. The decision to extend the dosing interval beyond a 24-hour period should be based on the need to maintain therapeutic peak or trough levels. The dosing interval may be prolonged if the peak level is most important. When the minimum trough level must be maintained, it is preferable to modify the individual dose or use a combination of dose and interval methods to determine the correct dosing strategy. Drugs removed by dialysis and given once daily should be given after the dialysis treatment.

Drug Removal by Dialysis

Hemodialysis (HD) removes drugs from plasma by diffusion across the dialysis membrane. Diffusion proceeds from higher concentrations in the plasma to lower concentrations in the dialysate. The drug, the dialysis procedure, and the patient influence the rate and extent of drug removal by dialysis. Drugs smaller than 500 Daltons readily cross standard dialysis membranes. Dialysis does not remove drugs that are > 90 % protein bound or drugs with large volumes of distribution. Porous membranes, used for continuous renal replacement therapies, allow the filtration of much larger drugs. Since HD removes drugs by diffusion, large surface area dialyzers, increasing the blood flow rate, increasing the dialysate flow rate, and lengthening the duration of the treatment increase the amount of drug removed. The following relationship estimates the hemodialysis clearance of a drug:

$C_{HD} = C_{urea} \times (60/MW_{drug})$

where C_{HD} is the drug's clearance by hemodialysis, C_{urea} is the clearance of urea by the dialyzer, and MW_{drug} is the molecular weight of the drug [13]. The urea clearance for most standard dialyzers is about 150 mL/min.

The efficiency of drug removal by peritoneal dialysis (PD) is much less than during HD [14]. Drug removal by PD is most effective for smaller molecular weight drugs, drugs that are not extensively bound to serum proteins, and drugs distributed in the extracellular fluid. The rate and extent of small molecular weight drug removal depends on the volume of peritoneal dialysate exchanged. The following relationship estimates peritoneal drug clearance:

$$C_{PD} = C_{urea} \times \frac{\sqrt{60}}{\sqrt{MW_{drug}}}$$

where C_{PD} is the peritoneal drug clearance; C_{urea} is the peritoneal urea clearance; and MW_{drug} is the molecular weight of the drug. Peritoneal urea clearance is approximately 20 mL/min. In general, if a drug is not removed by HD, it will not be removed by PD.

Table 1 lists drugs frequently used in dialysis patients and the appropriate dosage adjustments. Suggestions for reducing the individual doses, prolonging the dose interval, or a combination of the methods are included. Recommendations for supplemental doses following HD and during CAPD are listed [15].

When medications are added to peritoneal dialysate, drug transport across the peritoneal membrane is unidirectional [16]. The addition of drugs to peritoneal dialysate results in high drug concentrations in the dialysis fluid relative to the blood. Although peritoneal dialysis does not rapidly remove drugs, many are well absorbed when placed in peritoneal dialysate because of the resulting large concentration gradient between the dialysate and the blood.

The rate and extent of drug removal by continuous renal replacement therapies (CRRT) depends on the drugs molecular weight, membrane characteristics, blood flow rate, and the addition of dialysate to the extracorporeal circuit. Molecular weight affects drug removal by diffusion during dialysis more than during convection during CRRT because of the large pore size of membranes used for CRRT. Since most drugs have a molecular weight < 1,500 Daltons, drug removal by CRRT does not depend greatly on molecular weight.

A drugs volume of distribution and binding to serum proteins are the most important factors determining removal by CRRT. Drugs with a large volume of distribution are highly tissue bound and not accessible to extracorporeal circuit in quantities sufficient to result in substantial removal by CRRT. Even if the extraction across the artificial membrane is 100%, only a small amount of a drug with a large volume of distribution is removed. A volume of distribution > 0.7 L/kg substantially decreases CRRT drug removal.

Drug protein binding also determines how much is removed during CRRT. Only unbound drug is available for elimination by CRRT. Protein binding > 80% is a substantial barrier to drug removal by convection or diffusion.

During continuous hemofiltration, a filtration rate of 10 – 30 mL/min is achieved. The addition of diffusion by continuous dialysis adds 15 – 20 mL/min. Therefore, continuous dialysis and continuous hemofiltration together provide a drug clearance 10 – 50 mL/min.

The use of porous membranes and high blood flow rates during routine HD have blurred the distinction in drug removal among renal replacement therapies. Little data are available on drug removal by these techniques. Results from studies in chronic, stable

Table 1. Dose Adjustment for Drugs Frequently Used in Dialysis Patients. Method refers to changing the dose amount (D) or the dose interval (I). Percentages are the percent of the dose for normal renal function. NA is listed for drugs where dosing is not applicable during renal replacement therapy.

Drug	Half-Life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Acarbose	3 – 9 / Prolonged	15	0.32
Acebutolol	7 – 9 / 7	20	1.2
Acetazolamide	1.7 – 5.8 / Unknown	70 – 90	0.2
Acetohexamide	1 – 1.3 / Unchanged	65 – 90	0.21
Acetohydroxamic acid	3.5 – 5 / 15 – 23	Unknown	Unknown
Acetaminophen	2 / 2	20 – 30	1 – 2
Acetylsalicylic acid (Aspirin)	2 – 3 / Unchanged	80 – 90	0.1 – 0.2
Acrivastine	1.4 – 2.1 / Unknown	50	0.6 – 0.7
Acyclovir	2.1 – 3.8 / 20	15 – 30	0.7
Adenosine	< 10 sec / Unchanged	0	Frage
Albuterol	2 – 4 / 4	7	2 – 2.5
Alcuronium	3 – 3.5 / 16	40	0.28 – 0.36
Alfentanil	1 – 3 / Unchanged	88 – 95	0.3 – 1
Allopurinol	2 – 8 / Unchanged	< 5	0.5
Alprazolam	9.5 – 19 / Unchanged	70 – 80	0.9 – 1.3
Alteplase (tPA)	0.5 / Unknown	Unknown	0.1
Altretamine	7 / Unknown	Unknown	Unknown
Amantadine	12 / 500	60	4 – 5
Amikacin	1.4 – 2.3 / 17 – 150	< 5	0.22 – 0.29
Amiloride	6 – 8 / 10 – 144	30 – 40	5 – 5.2
Amiodarone	14 – 120 days / Unchanged	96	70 – 140
Amitriptyline	24 – 40 / Unchanged	96	6 – 36
Amlodipine	35 – 50 / 50	> 95	21
Amoxapine	8 – 30 / Unknown	90	Unknown
Amoxicillin	0.9 – 2.3 / 5 – 20	15 – 25	0.26
Amphotericin	24 / Unchanged	90	4.0
Amphotericin B colloidal dispersion	24 – 30/? Unchanged	90	4.0
Amphotericin B lipid complex	19 – 45/? Unchanged	90	1.7 – 3.9
Ampicillin	0.8 – 1.5 / 7 – 20	20	0.17 – 0.31
Amrinone	2.6 – 8.3 / Unknown	20 – 40	1.3 – 1.6
Anistreplase	1.2	Unknown	.08
Astemizole	20 days / Unchanged	97	Unknown
Atenolol	6.7 / 15 – 35	3	1.1
Atovaquone	55 – 77/Unknown	99	Unknown
Atracurium	0.3 – 0.4 / Unchanged	82	0.15 – 0.18
Auranofin	70 – 80 days / Unknown	60	Unknown
Azathioprine	0.16 – 1 / Increased	20	0.55 – 0.8
Azithromycin	10 – 60 / ?	8 – 50	18
Azlocillin	0.8 – 1.5 / 5 – 6	30	0.18 – 0.27
Aztreonam	1.7 – 2.9 / 6 – 8	45 – 60	0.5 – 1.0
Benazepril	22 / 30	95	0.15
Bepridil	24 – 48 / 24 – 48	Unknown	Unknown
Betamethasone	5.5 / Unknown	65	1.4

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	Avoid	Unknown	Unknown	Avoid
D	30 – 50%	None	None	50%
I	Avoid	Unknown	Unknown	Avoid
I	Avoid	Unknown	None	Avoid
D	Avoid	Unknown	Unknown	Unknown
I	q8h	None	None	q6h
I	Avoid	Dose after dialysis	None	q4 – 6h
D	Unknown	Unknown	Unknown	Unknown
D,I	2.5 mg/kg q24h	Dose after dialysis	Dose for Renal Failure	3.5 mg/kg/day
D	100%	None	None	100%
D	50%	Unknown	Unknown	75%
D	Avoid	Unknown	Unknown	Avoid
D	100%	NA	NA	NA
D	25%	1/2 dose	Unknown	50%
D	100%	None	Unknown	NA
D	100%	Unknown	Unknown	100%
D	Unknown	Unknown	Unknown	Unknown
I	q7days	None	None	q48 – 72h
D,I	20% to 30% q24 – 48h	2/3 normal dose after dialysis	15 – 20 mg/L d	30 – 70% q12 – 18h
D	Avoid	NA	NA	NA
D	100%	None	None	100%
D	100%	None	Unknown	NA
D	100%	None	None	100%
D	100%	Unknown	Unknown	NA
I	q24h	Dose after dialysis	250 mg q12h	NA
I	q24 – 36h	None	Dose for Renal Failure	q24h
I	q 24 – 36h	None	Dose for Renal Failure	q 24h
I	q 24 – 36h	None	Dose for Renal Failure	q 24h
I	q12 – 24h	Dose after dialysis	250 mg q12h	q6 – 12h
D	50 – 75%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	NA
D,I	30 – 50% q96h Unknown: 100%	25 – 50 mg Unknown: None	None Unknown	50% q48h Unknown
D	100%	Unknown	Unknown	100%
D	Avoid	None	None	None
D	50%	Yes	Unknown	75%
D	100%	None	None	None
I	q8h	Dose after dialysis	Dose for Renal Failure	q6 – 8h
D	25%	0.5 g after dialysis	Dose for Renal Failure	50 – 75%
D	25 – 50% Unknown	None None	None None	50 – 75% Unknown
D	100%	Unknown	Unknown	100%

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Betamethasone	5.5 / Unknown	65	1.4
Betaxolol	15 – 20 / 30 – 35	45 – 60	5 – 10
Bezafibrate	2.1 / 7.8	95	0.24 – 0.3
Bisoprolol	9 – 13 / 18 – 24	30 – 35	3
Bleomycin	9 / 20	Unknown	0.3
Bleomycin	9 / 20	Unknown	0.3
Bopindolol	4 – 10 / Unchanged	Unknown	2 – 3
Bretylium	6 – 13.6 / 16 – 32	6	8.2
Bromocriptine	3 / Unknown	90 – 96	Unknown
Brompheniramine	6 / Unknown	Unknown	12
Budesonide	2 – 2.7 / Unknown	88	4.3
Bumetanide	1.2 – 1.5 / 1.5	96	0.2 – 0.5
Bupropion	10 – 21 / Unknown	82 – 88	27 – 36
Buspirone	2 – 3 / 5.8	95	5.0
Busulfan	2.5 – 3.4 / Unknown	3 – 15	1.0
Butorphanol	2 – 4 / Unknown	80	9 – 11
Capreomycin	2 / Unknown	Unknown	Unknown
Captopril	2 – 3 / 21 – 32	25 – 30	0.7 – 3
Carbamazepine	24 single; 4 – 6 chronic dosing	75	0.8 – 1.6
Carbidopa	2 / Unknown	Unknown	Unknown
Carboplatin	6 / Increased	15 – 24	0.23 – 0.28
Carmustine	1.5 / Unknown	Unknown	3.3
Carteolol	7 / 33	20 – 30	4.0
Carvedilol	5 – 8 / 5 – 8	95	1 – 2
Cefaclor	1 / 3	25	0.24 – 0.35
Cefadroxil	1.4 / 22	20	0.31
Cefamandole	1 / 6 – 11	75	0.16 – 0.25
Cefazolin	2 / 40 – 70	80	0.13 – 0.22
Cefepime	2.2 / 18	16	0.3
Cefixime	3.1 / 12	50	0.6 – 0.11
Cefmenoxime	0.8 – 1.3 / 6 – 12	43 – 75	0.27 – 0.37
Cefmetazole	1.2 / 21	75	0.18
Cefonicid	4 / 17 – 59	96	0.09 – 0.18
Cefoperazone	1.6 – 2.5 / 2.9	90	0.14 – 0.20
Ceforanide	3 / 25	80	0.17
Cefotaxime	1 / 15	37	0.15 – 0.55
Cefotetan	3.5 / 13 – 25	85	0.15
Cefoxitin	1 / 13 – 23	41 – 75	0.2
Cefpodoxime	2.5 / 26	26	0.6 – 1.2
Cefprozil	1.7 / 6	40	0.65
Ceftazidime	1.2 / 13 – 25	17	0.28 – 0.4
Ceftibutin	1.5 – 2.7/22	70	0.2
Ceftizoxime	1.4 / 35	28 – 50	0.26 – 0.42
Ceftriaxone	7 – 9 / 12 – 24	90	0.12 – 0.18

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	100%	Unknown	Unknown	100%
D	50%	None	None	100%
D	25%	Unknown	Unknown	50%
D	50%	Unknown	Unknown	75%
D	50%	None	Unknown	75%
D	50%	None	Unknown	Unknown
D	100%	None	None	100%
D	25%	None	None	25 – 50%
D	100%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	NA
D	100%	Unknown	Unknown	100%
D	100%	None	None	NA
D	100%	Unknown	Unknown	NA
D	100%	None	Unknown	NA
D	100%	Unknown	Unknown	100%
D	50%	Unknown	Unknown	NA
I	q48h	Give dose after HD only	None	q24h
D,I	50% q24h	25 – 30%	None	75% q12 – 18h
D	100%	None	None	None
D	100%	Unknown	Unknown	Unknown
D	25%	1/2 dose	Unknown	50%
D	Unknown	Unknown	Unknown	Unknown
D	25%	Unknown	None	50%
D	100%	None	None	100%
D	50%	250 mg after dialysis	250 mg q8 – 12h	NA
I	q24 – 48h	0.5 – 1.0 g after dialysis	0.5 g/day	NA
I	q12h	0.5 – 1.0 g after dialysis	0.5 – 1.0 g q12h	q6 – 8h
I	q24 – 48h	0.5 – 1.0 g after dialysis	0.5 g q12h	q12h
I	q24 – 48h	1.0 g after dialysis	Dose for Renal Failure	Not recommended
D	50%	300 mg after dialysis	200 mg/day	Not recommended
D,I	0.75 g q12h	0.75 g after dialysis	0.75 g q12h	0.75 g q8h
I	q48h	Dose after dialysis	Dose for Renal Failure	q24h
D,I	0.1 g/day	None	None	None
D	100%	1 g after dialysis	None	None
I	q24 – 48h	0.5 – 1.0 g after dialysis	None	1.0 g/day
I	q24h	1 g after dialysis	1 g/day	1 g q12h
D	25%	1 g after dialysis	1 g/day	750 mg q12h
I	q24 – 48h	1 g after dialysis	1 g/day	q8 – 12h
I	q24 – 48h	200 mg after dialysis only	Dose for Renal Failure	NA
D,I	250 mg q24h	250 mg after dialysis	Dose for Renal Failure	Dose for Renal Failure
I	q48h	1 g after dialysis	0.5 g/day	q24 – 48h
D	25%	300 mg after dialysis only	Dose for Renal Failure	50%
I	q24h	1 g after dialysis	0.5 – 1.0 g/day	q12 – 24h
D	100%	Dose after dialysis	750 mg q12h	100%

I.19

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Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Cefuroxime axetil	1.2 / 17	35 – 50	0.13 – 1.8
Cefuroxime sodium	1.2 / 17	33	0.13 – 1.8
Celiprolol	4 – 5 / 5	Unknown	Unknown
Cephalexin	0.7 / 16	20	0.35
Cephalothin	0.5 – 1 / 3 – 18	65	0.26
Cephapirin	0.4 / 2.5	45 – 60	0.22
Cephradine	0.7 – 1.3 / 6 – 15	10	0.25 – 0.46
Cetirizine	7 – 10 / 20	93	0.4 – 0.6
Chloral hydrate	7 – 14 / Unknown	70 – 80	0.6
Chlorambucil	1 / Unknown	Unknown	0.86
Chloramphenicol	1.6 – 3.3 / 3 – 7	45 – 60	0.5 – 1.0
Chlorazepate (Tranxene)	39 – 85 / 36	Unknown	1.3
Chlordiazepoxide (Librium)	5 – 30 / Unchanged	94 – 97	0.3 – 0.5
Chloroquine	2 – 4 / 5 – 50 days	50 – 65	Large
Chlorpheniramine	14 – 24 / Unknown	72	6 – 12
Chlorpromazine	11 – 42 / Unchanged	91 – 99	8 – 160
Chlorpropamide	24 – 48 / 50 – 200	88 – 96	.09 – 0.27
Chlorthalidone	44 – 80 / Unknown	76 – 90	3.9
Cholestyramine	Not absorbed	None	None
Cibenzoline	7 / 22	50	4 – 5
Cidofovir	2.5/Unknown	< 6	0.3 – 0.8
Cilastin	1 / 12	44	0.22
Cilazapril	40 – 50 / > 60	Unknown	0.5 – 0.8
Cimetidine	1.5 – 2 / 5	20	0.8 – 1.3
Cinoxacin	1.2 / 12	63	0.25
Ciprofloxacin	3 – 6 / 6 – 9	20 – 40	2.5
Cisapride	7 – 10 / Unchanged	98	2.4
Cisplatin	0.3 – 0.5 / Unknown	90	0.5
Cladribine	7 – 14 / Unknown	Unknown	50 – 80
Clarithromycin	2.3 – 6 / Unknown	70	2 – 4
Clavulanic acid	1 / 3 – 4	30	0.3
Clindamycin	2 – 4 / 3 – 5	60 – 95	0.6 – 1.2
Clodronate	13 / Increased	36	0.25
Clofazamine	10 – 70 days (?)/Unknown	Unknown	Unknown
Clofibrate	15 – 17.5 / 30 – 110	92 – 97	0.14
Clomipramine	19 – 37 / Unknown	97	Unknown
Clonazepam (clonopin)	18 – 50 / Unknown	47	1.5 – 4.5
Clonidine	6 – 23 / 39 – 42	20 – 40	3 – 6
Codeine	2.5 – 3.5 / Unknown	7	3 – 4
Colchicine	19 / 40	31	2.2
Colestipol	Not absorbed	None	None
Cortisone	0.5 – 2 / 3.5	90	Unknown
Cyclophosphamide	4 – 7.5 / 10	14 – 20	0.5 – 1
Cycloserine	0.5 / Unknown	Unknown	0.11 – 0.26
Cyclosporine	3 – 16 / Unchanged	96 – 99	3.5 – 7.4
Cytarabine	0.5 – 3 / Unchanged	13	2.6

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	100%	Dose after dialysis	Dose for Renal Failure	NA
I	q12h	Dose after dialysis	Dose for Renal Failure	1 g q12h
D	75%	Unknown	None	100%
I	q12h	Dose after dialysis	Dose for Renal Failure	NA
I	q12h	Dose after dialysis	1 g q12h	1 g q8h
I	q12h	Dose after dialysis	1 g q12h	1 g q8h
D	25%	Dose after dialysis	Dose for Renal Failure	NA
D	30%	None	Unknown	NA
D	Avoid	None	Unknown	NA
D	Unknown	Unknown	Unknown	Unknown
D	100%	None	None	None
D	100%	Unknown	Unknown	NA
D	50%	None	Unknown	100%
D	50%	None	None	None
D	100%	None	Unknown	NA
D	100%	None	None	100%
D	Avoid	Unknown	None	Avoid
I	Avoid	NA	NA	NA
D	100%	None	None	100%
D,I	66% q24h	None	None	100% q12h
D	Unknown: avoid	Unknown	Unknown	Unknown, Avoid
D	Avoid	Avoid	Avoid	Avoid
D,I	10 – 25% q72h	None	None	50% q24 – 48h
D	25%	None	None	50%
D	Avoid	Avoid	Avoid	Avoid
D	50%	250 mg q12h (200 mg if IV)	250 mg q8h (200 mg if IV)	200 mg IV q12h
D	50%	Unknown	Unknown	50 – 100%
D	50%	Yes	Unknown	75%
D	Unknown	Unknown	Unknown	Unknown
D	50 – 75%	Dose after dialysis	None	None
D	50 – 75%	Dose after dialysis	Dose for Renal Failure	100%
D	100%	None	None	None
D	Avoid	Unknown	Unknown	Unknown
	Unknown	Unknown	Unknown	Unknown
I	Avoid	None	Unknown	q12 – 18h
D	Unknown	Unknown	Unknown	NA
D	100%	None	Unknown	NA
D	100%	None	None	100%
D	50%	Unknown	Unknown	75%
D	50%	None	Unknown	100%
D	100%	None	None	100%
D	100%	None	Unknown	100%
D	75%	1/2 dose	Unknown	100%
I	q24h	None	None	q12 – 24h
D	100%	None	None	100%
D	100%	Unknown	Unknown	100%

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Dapsone	20 – 30/Unknown	70 – 90	1 – 1.5
Daunorubicin	18 – 27 / Unknown	Unknown	Unknown
Delavirdine	5.8 / Unknown	98	0.5
Deferoxamine	6 / Unknown	Unknown	2 – 2.5
Desipramine	18 – 26 / Unknown	92	10 – 50
Dexamethasone	3 – 4 / Unknown	70	0.8 – 1
Diazepam (Valium)	20 – 90 / Unchanged	94 – 98	0.7 – 3.4
Diazoxide	17 – 31 / 30 – 60	> 90	0.2 – 0.3
Diclofenac	1 – 2 / Unchanged	> 99	0.12 – 0.17
Dicloxacillin	0.7 / 1 – 2	95	0.16
Didanosine	0.6 – 1.6 / 4.5	< 5	1.0
Diflunisal	5 – 20 / 62	> 99	0.1 – 0.13
Digitoxin	144 – 200 / 210	94	0.6
Digoxin	36 – 44 / 80 – 120	20 – 30	5 – 8
Dilevalol	8 – 12 / 19 – 30	75	25
Diltiazem	2 – 8 / 3.5	98	9 – 10
Diphenhydramine	3.4 – 9.3 / Unknown	80	3.3 – 6.8
Dipyridamole	12 / Unknown	99	2.4
Dirithromycin	30 – 44 / Unknown	15 – 30	> 10
Disopyramide	5 – 8 / 10 – 18	54 – 81	0.8 – 2.6
Dobutamine	2 min / Unknown	Unknown	0.25
Doxacurium	1.2 – 1.6 / 3.7	28 – 34	0.12 – 0.22
Doxazosin	16 – 22 / 16 – 22	98	1 – 1.7
Doxepin	8 – 25 / 10 – 30	95	9 – 33
Doxorubicin	35 / Unchanged	80 – 85	21.5
Doxycycline	15 – 24 / 18 – 25	80 – 90	0.75
Dyphylline	1.8 – 2.3 / 12	< 3	0.8
Enalapril	11 – 24 / 34 – 60	50 – 60	Unknown
Epirubicin	35 / 35	80 – 85	10 – 40
Erbastine	13 – 16 / 23 – 26	98	1 – 2
Erythromycin	1.4 / 5 – 6	60 – 95	0.6 – 1.2
Esmolol	7 – 15 min / Unchanged		
Estazolam	8 – 24 / Unknown	93	Unknown
Ethacrynic acid	2 – 4 / Unknown	90	0.1
Ethambutol	4 / 7 – 15	10 – 30	1.6 – 3.2
Ethchlorvynol	10 – 20	35 – 50	3 – 4
Ethionamide	2.1	30	Unknown
Ethosuximide	35 – 55 / Unchanged	10	0.6 – 0.9
Etodolac	5 – 7 / Unchanged	> 99	0.4
Etomidate	4 – 5 / Unchanged	75	2 – 4.5
Etoposide	4 – 8 / 19	74 – 94	0.17 – 0.5
Famciclovir	1.6 – 2.9/10 – 22	< 25%	1.5
Famotidine	2.5 – 4 / 12 – 19	15 – 22	0.8 – 1.4
Fazadinium	1 / Unchanged	17	0.18 – 0.23
Felodipine	10 – 14 / 21 – 24	99	9 – 10

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
	Unknown	Unknown: None	Dose for Renal Failure	Unknown
D	100%	Unknown	Unknown	Unknown
	Unknown: 100%	Unknown: None	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	100%	None	None	NA
D	100%	Unknown	Unknown	100%
D	100%	None	Unknown	100%
D	100%	None	None	100%
D	100%	None	None	100%
D	100%	None	None	NA
I	q24 – 48h	Dose after dialysis	Dose for Renal Failure	Dose for Renal Failure
D	50%	None	None	50%
D	50 – 75%	None	None	100%
D,I	10 – 25% q48h	None	None	25 – 75% q36h
D	100%	None	None	Unknown
D	100%	None	None	100%
D	100%	None	None	None
D	100%	Unknown	Unknown	NA
	100%	None	Unknown	100%
I	q24 – 40h	None	None	q12 – 24h
D	100%	Unknown	Unknown	100%
D	50%	Unknown	Unknown	50%
D	100%	None	None	100%
D	100%	None	None	100%
D	100%	None	Unknown	100%
D	100%	None	None	100%
D	25%	1/3 dose	Unknown	50%
D	50%	20 – 25%	None	75 – 100%
D	100%	None	Unknown	100%
D	50%	Unknown	Unknown	50%
D	50 – 75%	None	None	None
		None	None	Unknown
D	100%	Unknown	Unknown	NA
I	Avoid	None	None	NA
I	q48h	Dose after dialysis	Dose for Renal Failure	q24 – 36h
D	Avoid	None	None	NA
D	50%	None	None	None
D	100%	None	Unknown	Unknown
D	100%	None	None	100%
D	100%	Unknown	Unknown	100%
D	50%	None	Unknown	75%
I	50% q 48 h	Dose after dialysis	Unknown	Unknown
D	10%	None	None	25%
D	100%	Unknown	Unknown	100%
D	100%	None	None	100%

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Fenoprofen	2 – 3 / Unchanged	> 99	0.1
Fentanyl	2.5 – 3.5 / Unchanged	79 – 87	2 – 5
Fexofenadine	14 / 19 – 25	70	Unknown
Flecainide	12 – 19.5 / 19 – 26	52	8.4 – 9.5
Fleroxacin	13 / 21 – 28	20	1.1 – 2.4
Fluconazole	22 / Unknown	12	0.7
Flucytosine	3 – 6 / 75 – 200	< 10	0.6
Fludarabine	7 – 12 / 24	Unknown	5 – 40
Flumazenil	0.7 – 1.3 / Unknown	40 – 50	0.6 – 1.1
Flunarizine	17 – 18 d / Unknown	99	43 – 78
Fluorouracil	0.1 / Unchanged	10	0.25 – 0.5
Fluoxetine (Prozac)	24 – 72 / Unchanged	94.5	12 – 42
Flurazepam (Dalmane)	47 – 100 / Unchanged	Unknown	3.4
Flurbiprofen	3 – 5 / Unchanged	99	0.1
Flutamide	4 – 6 / Unknown	Unknown	Unknown
Fluvastatin	0.5 – 1 / Unknown	Unknown	0.42
Fluvoxamine (Luvox)	12 – 15 / Unchanged	77	25
Foscarnet	3 / Prolonged (up to 100 hours)	17	0.3 – 0.6
Fosinopril	12 / 14 – 32	95	0.15
Furosemide	0.5 – 1.1 / 2 – 4	95	.07 – 0.2
Gabapentin	5 – 7 / 132	Unbound	0.7
Gallamine	2.3 – 2.7 / 6 – 20	30 – 70	0.21 – 0.24
Ganciclovir	3.6 / 30	Unknown	0.47
Ganciclovir-oral			
Gemfibrozil	7.6 / Unchanged	97 – 99	Unknown
Gentamicin	1.8 / 20 – 60	< 5	0.23 – 0.26
Glibornuride	5 – 12 / Unknown	95	0.25
Gliclazide	8 – 11 / Unknown	85 – 95	0.24
Glipizide	3 – 7 / Unknown	97	0.13 – 0.16
Glyburide	1.4 – 2.9 / Unknown	99	0.16 – 0.3
Gold sodium thiomalate	250 d / Unknown	95	5 – 9
Griseofulvin	14 / 20	Unknown	1.6
Guanabenz	12 – 14 / Unknown	90	10 – 12
Guanadrel	4 – 10 / 19	20	11.5
Guanethidine	120 – 140 / Unknown	< 5	Unknown
Guanfacine	12 – 23 / 15 – 25	65	4 – 6.5
Haloperidol	10 – 19 / Unknown	90 – 92	14 – 21
Heparin	0.3 – 2 / Unchanged	> 90	0.06 – 0.1
Hexobarbital	3.5 – 4 / Unknown	65	1.1
Hydralazine	2 – 4.5 / 7 – 16	87	0.5 – 0.9
Hydrocortisone	1.5 – 2 / Unknown	Unknown	Unknown
Hydroxyurea	Unknown	Unknown	0.5
Hydroxyzine	14 – 20 / Unknown	Unknown	19.5

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	100%	None	None	100%
D	100%	NA	NA	NA
I	q24h	Unknown	Unknown	q12 – 24h
D	50 – 75%	None	None	100%
D	50%	400 mg after dialysis	400 mg/day	NA
D	100%	200 mg after dialysis	Dose for Renal Failure	100%
I	q24h	Dose after dialysis	0 .5 – 1.0 g/day	q16h
D	50%	Unknown	Unknown	75%
D	100%	None	Unknown	NA
D	100%	None	None	None
D	100%	Yes	Unknown	100%
D	100%	Unknown	Unknown	NA
D	100%	None	Unknown	NA
D	100%	None	None	100%
D	100%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	100%	None	Unknown	NA
D	6 mg/kg	Dose after dialysis	Dose for Renal Failure	15 mg/kg
D	75% to 100%	None	None	100%
D	100%	None	None	NA
D,I	300 mg qd	300mg load, then 200 – 300 after each dialysis		300q 12 – 24h
D	Avoid	NA	NA	Avoid
I	q48 – 96h	Dose after dialysis	Dose for Renal Failure	2.5 mg/kg day
D,I	Unknown: 500 mg q 48 – 96h	Unknown:Dose after dialysis	Dose for Renal Failure	NA
D	100%	None	Unknown	100%
D,I	20 – 30% q24 – 48h	2/3 normal dose after dialysis	3 – 4 mg/L day	30 – 70% q12h
D	Unknown	Unknown	Unknown	Avoid
D	Unknown	Unknown	Unknown	Avoid
D	100%	Unknown	Unknown	Avoid
D	Avoid	None	None	Avoid
D	Avoid	None	None	Avoid
D	100%	None	None	None
D	100%	Unknown	Unknown	100%
I	q24 – 48h	Unknown	Unknown	q12 – 24h
I	q24 – 36h	Unknown	Unknown	Avoid
D	100%	None	None	100%
D	100%	None	None	100%
D	100%	None	None	100%
D	100%	None	Unknown	NA
I	q8 – 16h	None	None	q8h
D	100%	Unknown	Unknown	100%
D	20%	Unknown	Unknown	50%
D	Unknown	100%	100%	100%

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Ibuprofen	2 – 3.2 / Unchanged	99	0.15 – 0.17
Idarubicin	36 – 70 / Unknown	Unknown	Unknown
Ifosfamide	4 – 10 / Unknown	Unknown	0.4 – 0.64
Iloprost	0.3 – 0.5 / Unknown	Unknown	0.7
Imipenem	1 / 4	13 – 21	0.17 – 0.3
Imipramine	12 – 24 / Unknown	96	10 – 20
Indapamide	14 – 18 / Unchanged	76 – 79	0.3 – 1.3
Indinavir	1.8 / Unknown	60	Unknown
Indobufen	6 – 7 / 27 – 33	> 99	0.18 – 0.2
Indomethacin	4 – 12 / Unchanged	99	0.12
Insulin	2 – 4 / Increased	5	0.15
Ipratropium	1.6 / Unknown	Unknown	4.6
Isoniazid	0.7 – 4 / 8 – 17	4 – 30	0.75
Isosorbide	0.15 – 0.5 / 4	72	1.5 – 4
Isradipine	1.9 – 4.8 / 10 – 11	97	3 – 4
Itraconazole	21 / 25	99	10
Kanamycin	1.8 – 5 / 40 – 96	< 5	0.19 – 0.23
Ketamine	2 – 3.5 / Unchanged	Unknown	1.8 – 3.1
Ketanserin	14 – 19 / 25 – 35	95	3 – 6
Ketoconazole	1.5 – 3.3 / 3.3	99	1.9 – 3.6
Ketoprofen	1.5 – 4 / Unchanged	99	0.11
Ketorolac	4 – 6 / 10	> 99	0.13 – 0.25
Labetolol	3 – 9 / Unchanged	50	5.6
Lamivudine	5 – 11 / 20	36	0.83
Lamotrigine	25 – 30 / Unknown	0.55	0.9 – 1.3
Lansoprazole	1.3 – 2.9 / Unchanged	> 98	Unknown
Levodopa	0.8 – 1.6 / Unknown	5 – 8	0.9 – 1.6
Levofloxacin	4 – 8 / 76	24 – 38	1.1 – 1.5
Lidocaine	2 – 2.2 / 1.3 – 3	60 – 66	1.3 – 2.2
Lincomycin	4 – 5 / 10 – 20	70 – 80	0.31 – 0.6
Lisinopril	30 / 40 – 50	0 – 10	0.13 – 0.15
Lispro Insulin	1 / Prolonged	Unknown	0.26 – 0.36
Lithium carbonate	14 – 28 / 40	None	0.5 – 0.9
Lomefloxacin	8 / 44	15	1.8 – 3.1
Loracarbef	0.8 – 1.3 / 32	25	0.3 – 0.4
Lorazepam (Ativan)	5 – 10 / 32 – 70	87	0.9 – 1.3
Losartan	3 / 4 – 6	30	0.4
Lovastatin	1.1 – 1.7 / Unchanged	> 95	Unknown
Low-molecular-weight heparin	2.2 – 6 / 3.6 – 5	Unknown	0.06 – 0.13
Maprotiline (Ludiomil)	48 / Unknown	Unknown	Unknown
Meclofenamic acid	3 / Unchanged	> 99	Unknown
Mefenamic acid	3 – 4 / Unchanged	Unknown	Unknown

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	100%	None	None	100%
	Unknown	Unknown	Unknown	Unknown
D	75%	Unknown	Unknown	100%
D	50%	Unknown	Unknown	100%
D	25%	Dose after dialysis	Dose for Renal Failure	50%
D	100%	None	None	NA
D	Avoid	None	None	NA
	100%	None	Dose for Renal Failure	Unknown
D	25%	Unknown	Unknown	NA
D	100%	None	None	100%
D	50%	None	None	75%
D	100%	None	None	100%
D	50%	Dose after dialysis	Dose for Renal Failure	Dose for Renal Failure
D	100%	10 – 20 mg	None	100%
D	100%	None	None	100%
D	50%	100 mg q12 – 24h	100 mg q12 – 24h	100 mg q12 – 24h
D,I	20 – 30% q24 – 48h	2/3 normal dose after dialysis	15 – 20 mg/L d	30 – 70% q12H
D	100%	Unknown	Unknown	100%
D	100%	None	None	100%
D	100%	None	None	None
D	100%	None	None	100%
D	50%	None	None	50%
D	100%	None	None	100%
D,I	25 mg qd (50 mg first dose)	Dose after dialysis	Dose for Renal Failure	50 – 150 mg qd (full first dose)
	100%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	25 – 50%	Dose for Renal Failure	Dose for Renal Failure	50%
D	100%	None	None	100%
I	q12 – 24h	None	None	NA
D	25 – 50%	20%	None	50 – 75%
D	50%	None	None	None
D	25 – 50%	Dose after dialysis	None	50 – 75%
D	50%	Dose for Renal Failure	Dose for Renal Failure	NA
I	q3 – 5days	Dose after dialysis	Dose for Renal Failure	q24h
D	100%	None	Unknown	100%
D	100%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	100%
D	50%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	NA
D	100%	None	None	100%
D	100%	None	None	100%

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Mefloquine	15 – 33 days / Unknown	98	20
Melphalan	1.1 – 1.4 / 4 – 6	90	0.6 – 0.75
Meperidine (Demerol)	2 – 7 / 7 – 32	70	4 – 5
Meprobamate	9 – 11 / Unchanged	0 – 30	0.5 – 0.8
Meropenem	1.1 / 6 – 8	Low	0.35
Metaproterenol	2 – 6 / Unknown	10	7.6
Metformin	1 – 5 / Prolonged	Negligible	1 – 4
Methadone	13 – 58 / Unknown	60 – 90	3 – 6
Methenamine mandelate	4 / Unknown	Unknown	Unknown
Methicillin	0.5 – 1 / 4	35 – 60	0.31
Methimazole	3 – 6 / Unchanged	None	0.6
Methotrexate	8 – 12 / Increased	45 – 50	0.76
Methyldopa	1.5 – 6 / 6 – 16	< 15	0.5
Methylprednisolone	1.9 – 6 / Unchanged	40 – 60	1.2 – 1.5
Metoclopramide	2.5 – 4 / 14 – 15	40	2 – 3.4
Metocurine	3.5 – 5.8 / 11.3	70	0.42 – 0.57
Metolazone	4 – 20 / Unknown	95	1.6
Metoprolol	3.5 / 2.5 – 4.5	8	5.5
Metronidazole	6 – 14 / 7 – 21	20	0.25 – 0.85
Mexiletine	8 – 13 / 16	70 – 75	5.5 – 6.6
Mezlocillin	0.6 – 1.2 / 2.6 – 5.4	20 – 46	0.18
Miconazole	20 – 24 / Unchanged	90	Large
Midazolam	1.2 – 12.3 / Unchanged	93 – 96	1.0 – 6.6
Midodrine	0.5 / Unknown	Unknown	Unknown
Miglitol	3 – 5 / Prolonged	Unknown	Unknown
Milrinone	1 / 1.5 – 3	Unknown	0.25 – 0.35
Minocycline	12 – 16 / 12 – 18	70	1.0 – 1.5
Minoxidil	2.8 – 4.2 / Unchanged	0	2 – 3
Mitomycin C	0.5 – 1 / Unknown	Unknown	0.5
Mitoxantrone	23 – 40 / Unknown	75	200 – 300
Mivacurium	1.5 – 3	Unknown	0.1
Moricizine	2 / 3	95	> 5.0
Morphine	1 – 4 / Unchanged	20 – 30	3.5
Moxalactam (Latamoxef)	2.3 / 18 – 23	35 – 59	0.18 – 0.4
Nabumetone	24 / Unchanged	> 99	0.11
N-Acetylcysteine	2.3 – 6 / Unknown	50	0.33 – 0.47
N-Acetyl-procainamide	6 – 8 / 42 – 70	10 – 20	1.5 – 1.7
Nadolol	19 / 45	28	1.9
Nafcillin	0.5 / 1.2	85	0.35
Nalidixic acid	6 / 21	90	0.25 – 0.35
Naloxone	1 – 1.5 / Unknown	54	3
Naproxen	12 – 15 / Unchanged	99	0.1
Nefazodone (Serzone)	2 – 4 / Unchanged	99	0.22 – 0.87
Nelfinavir	1.8 – 3.4 / Unknown	Unknown	Unknown
Neostigmine	1.3 / 3.0	None	0.5 – 1.0

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
	100%	None	None	Unknown
D	50%	Unknown	Unknown	75%
D	50%	Avoid	None	Avoid
I	q12 – 18h	None	Unknown	NA
D,I	250 – 500 mg q24h	Dose after dialysis	Dose for Renal Failure	250 – 500 mg q12h
D	100%	Unknown	Unknown	100%
D	Avoid	Unknown	Unknown	Avoid
D	50 – 75%	None	None	NA
D	Avoid	NA	NA	NA
I	q8 – 12h	None	None	q6 – 8h
D	100%	Unknown	Unknown	100%
D	Avoid	None	None	50%
I	q12 – 24h	250 mg	None	q8 – 12h
D	100%	Yes	Unknown	100%
D	50%	None	Unknown	50 – 75%
D	50%	Unknown	Unknown	50%
D	100%	None	None	NA
D	100%	50 mg	None	100%
D	50%	Dose after dialysis	Dose for Renal Failure	100%
D	50 – 75%	None	None	None
I	q8h	None	None	q6 – 8h
D	100%	None	None	None
D	50%	NA	NA	NA
	Unknown	5mg q8h	Unknown	5 – 10mg q8h
D	Avoid	Unknown	Unknown	Avoid
D	50 – 75%	Unknown	Unknown	100%
D	100%	None	None	100%
D	100%	None	None	100%
D	75%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	50%	Unknown	Unknown	Unknown
D	100%	None	None	100%
D	50%	None	Unknown	75%
I	q24 – 48h	Dose after dialysis	Dose for Renal Failure	q12 – 24h
D	100%	None	None	100%
D	75%	Unknown	Unknown	100%
D,I	25% q12 – 18h	None	None	50% q8 – 12h
D	25%	40 mg	None	50%
D	100%	None	None	100%
D	Avoid	Avoid	Avoid	NA
D	100%	NA	NA	100%
D	100%	None	None	100%
D	100%	Unknown	Unknown	NA
	Unknown	Unknown	Unknown	Unknown
D	25%	Unknown	Unknown	50%

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Netlimicin	1 – 3 / 35 – 72	< 5	0.16 – 0.30
Nevirapine	40 / ?	60	1.2 – 1.4
Nicardipine	5 / 5 – 7	98 – 99	0.8
Nicotinic acid	0.5 – 1 / Unknown	Unknown	Unknown
Nifedipine	4 – 5.5 / 5 – 7	97	1.4
Nimodipine	1 – 2.8 / 22	98	0.9 – 2.3
Nisoldipine	6.6 – 7.9 / 6.8 – 9.7	99	2.3 – 7.1
Nitrazepam	18 – 36 / Unknown	Unknown	Unknown
Nitrofurantoin	0.5 / 1	20 – 60	0.3 – 0.7
Nitroglycerine	2 – 4 min / Unchanged	Unknown	2 – 3
Nitroprusside	< 10 min / < 10 min	0	0.2
Nitrosoureas	Short / Unknown	Unknown	Unknown
Nizatidine	1.3 – 1.6 / 5.3 – 8.5	28 – 35	0.8 – 1.3
Norfloxacin	3.5 – 6.5 / 8	14	< 0.5
Nortriptyline (Pamelor)	25 – 38 / 15 – 66	95	15 – 23
Ofloxacin	5 – 8 / 28 – 37	25	1.5 – 2.5
Omeprazole	0.5 – 1 / Unchanged	95	Unknown
Ondansetron	2.5 – 5.5 / Unchanged	75	2
Orphenadrine	16 / Unknown	Unknown	Unknown
Ouabain	21 / 60 – 70	40	Unknown
Oxaproxin	50 – 60 / Unchanged	> 99	0.2
Oxatomide	20 / Unknown	91	Unknown
Oxazepam (Serax)	5 – 10 / 25 – 90	97	0.6 – 1.6
Oxcarbazepine	8 – 9 / Unknown	40	0.7 – 0.8
Paclitaxel	9 – 30 / Unknown	Unknown	30 – 60
Pancuronium	1.7 – 2.2 / 4.3 – 8.2	70 – 85	0.15 – 0.38
Paroxetine (Paxil)	10 – 16 / 30	95	13
PAS	1.0 / Unknown	15 – 50	0.11 – 24
Penbutolol	22 / 24	> 95	Unknown
Penicillamine	1.5 – 3 / Increased	80	Unknown
Penicillin G	0.5 / 6 – 20	50	0.3 – 0.42
Penicillin VK	0.6 / 4.1	50 – 80	0.5
Pentamidine	29 / 118	69	55 – 462
Pentazocine (Talwin)	2 – 5 / Unknown	50 – 75	5
Pentobarbital	18 – 48 / Unchanged	60 – 70	1.0
Pentopril	2 – 3 / 10 – 14	60	0.8
Pentoxifylline	0.8 / Unchanged	None	2.4 – 4.2
Perfloxacin	10 / 15	25 – 43	2.0
Perindopril	5 / 27	20	0.6 – 0.8
Phenelzine (Nardil)	1.5 – 4 / Unknown	Unknown	Unknown
Phenobarbital	60 – 150 / 117 – 160	40 – 60	0.7 – 1
Phenylbutazone	50 – 100 / Unchanged	99	0.09 – 0.17
Phenytoin	24 / Unchanged	90	1.0
Pindolol	2.5 – 4 / 3 – 4	50	1.2
Pipecuronium	2.3 / 4.4	Unknown	0.31

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D,I	10 – 20% q24 – 48h	2/3 normal dose after dialysis	3 – 4 mg/L/day	20 – 60% q12h
D	Unknown: 100%	Unknown: None	Dose for Renal Failure	Unknown
D	100%	None	None	100%
D	25%	Unknown	Unknown	50%
D	100%	None	None	100%
D	100%	None	None	100%
D	100%	None	None	100%
D	100%	Unknown	Unknown	NA
D	Avoid	NA	NA	NA
D	100%	Unknown	Unknown	100%
D	100%	None	None	100%
D	25 – 50%	None	Unknown	Unknown
D	25%	Unknown	Unknown	50%
I	Avoid	NA	NA	NA
D	100%	None	None	NA
D	25 – 50%	100 mg bid	Dose for Renal Failure	300 mg/day
D	100%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	NA
I	q36 – 48h	None	None	q24 – 36h
D	100%	None	None	100%
D	100%	None	None	NA
D	100%	None	Unknown	100%
D	100%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	Avoid	Unknown	Unknown	50%
D	50%	Unknown	Unknown	NA
D	50%	Dose after dialysis	Dose for Renal Failure	Dose for Renal Failure
D	100%	None	None	100%
D	Avoid	1/3 dose	Unknown	Avoid
D	20 – 50%	Dose after dialysis	Dose for Renal Failure	75%
D	100%	Dose after dialysis	Dose for Renal Failure	NA
I	q48h	None	None	None
D	50%	None	Unknown	75%
D	100%	None	Unknown	100%
D	50%	Unknown	Unknown	50 – 75%
D	100%	Unknown	Unknown	100%
D	100%	None	None	100%
D	50%	25 – 50%	Unknown	75%
D	100%	Unknown	Unknown	NA
I	q12 – 16h	Dose after dialysis	1/2 normal dose	q8 – 12h
D	100%	None	None	100%
D	100%	None	None	None
D	100%	None	None	100%
D	25%	Unknown	Unknown	50%

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Piperacillin	0.8 – 1.5 / 3.3 – 5.1	30	0.18 – 0.30
Piretanide	1.4 / 1.6 – 3.4	94	0.3
Piroxicam	45 – 55 / Unchanged	> 99	0.12 – 0.15
Plicamycin	2 / Unknown	Low	Unknown
Plicamycin	2 / Unknown	Low	Unknown
Pravastatin	0.8 – 3.2 / Unchanged	Unknown	Unknown
Prazepam	36 – 200 / 36	Unknown	Unknown
Prazosin	2 – 3 / 2 – 3	97	1.2 – 1.5
Prednisolone	2.5 – 3.5 / Unchanged	Saturable	2.2
Prednisone	2.5 – 3.5 / Unchanged	Saturable	2.2
Primaquine	4 – 7 / Unknown	Unknown	3 – 4
Primidone	5 – 15 / Unchanged	20 – 30	0.4 – 1
Probenecid	5 – 8 / Unchanged	85 – 95	0.15
Probucol	23 – 47 days / Unknown	Unknown	Unknown
Procainamide	2.5 – 4.9 / 5.3 – 5.9	15	2.2
Promethazine	12 / Unknown	93	13.5
Promethazine	9 – 12 / Unknown	Unknown	Large
Propafenone	5 / Unknown	> 95	3.0
Propofol	3 – 4.5 / Unchanged	Unknown	3.0 – 14.4
Propoxyphene (Darvon)	9 – 15 / 12 – 20	78	16
Propranolol	2 – 6 / 1 – 6	93	2.8
Propylthiouracil	1 – 2 / Unchanged	80	0.3 – 0.4
Protryptyline (Vivactil)	54 – 98 / Unknown	92	15 – 31
Pyrazinimide	9 / 26	5	0.75 – 1.3
Pyridostigmine	1.5 – 2 / 6	Unknown	0.8 – 1.4
Pyrimethamine	80 / Unchanged	27	2.9
Quazepam	20 – 40 / Unknown	95	Unknown
Quinapril	1 – 2 / 6 – 15	97	1.5
Quinidine	6 / 4 – 14	70 – 95	2 – 3.5
Quinine	5 – 16 / Unchanged	70	0.7 – 3.7
Ramipril	5 – 8 / 15	55 – 70	1.2
Ranitidine	1.5 – 3 / 6 – 9	15	1.2 – 1.8
Reserpine	46 – 168 / 87 – 323	96	Unknown
Ribavirin	30 – 60 / Unknown	0	9 – 15
Rifabutin	16 – 69 / Unchanged	71 – 89	8.2 – 9.3
Rifampin	1.5 – 5 / 1.8 – 11	60 – 90	0.9
Ritonavir	3 / Unknown	98 – 99	0.4
Saquinavir	12 / ?	98	10
Secobarbital	20 – 35 / Unknown	44	1.5 – 2.5
Sertraline (Zoloft)	24 / Unchanged	97	25
Simvastatin	Unknown	> 95	Unknown
Sodium valproate	6 – 15 / Unchanged	90	0.19 – 0.23
Sotalol	7.5 – 15 / 56	< 1	1.3
Sparfloxacin	15 – 20 / 38.5	35 – 55	4.5

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
I	q8h	Dose after dialysis	Dose for Renal Failure	q6 – 8h
D	100%	None	None	NA
D	100%	None	None	100%
D	50%	Unknown	Unknown	Unknown
D	50%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	NA
D	100%	None	None	100%
D	100%	Yes	Unknown	100%
D	100%	None	Unknown	100%
	100%	Unknown	Unknown	Unknown
I	q12 – 24h	1/3 dose	Unknown	Unknown
D	Avoid	Avoid	Unknown	Avoid
D	100%	Unknown	Unknown	100%
I	q8 – 24h	200 mg	None	q6 – 12h
D	100%	None	None	100%
D	100%	Unknown	Unknown	100%
D	100%	None	None	100%
D	100%	Unknown	Unknown	100%
D	Avoid	None	None	NA
D	100%	None	None	100%
D	100%	Unknown	Unknown	100%
D	100%	None	None	NA
D	Avoid	Avoid	Avoid	Avoid
D	20%	Unknown	Unknown	35%
D	100%	None	None	None
D	Unknown	Unknown	Unknown	NA
D	75%	25%	None	75 – 100%
D	75%	100 – 200 mg	None	100%
I	q24h	Dose after dialysis	Dose for Renal Failure	q8 – 12h
D	25 – 50%	20%	None	50 – 75%
D	25%	1/2 dose	None	50%
D	Avoid	None	None	100%
D	50%	Dose after dialysis	Dose for Renal Failure	Dose for Renal Failure
	100%	None	None	Unknown
D	50 – 100%	None	Dose for Renal Failure	Dose for Renal Failure
	100%	None	Dose for Renal Failure	Unknown
	100%	None	Dose for Renal Failure	Unknown
D	100%	None	None	NA
D	100%	Unknown	Unknown	NA
D	100%	Unknown	Unknown	100%
D	100%	None	None	None
D	15 – 30%	80 mg	None	30%
D,I	50% q 48h	dose for GFR < 10	Unknown	50 – 75%

→

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Spectinomycin	1.6 / 16 – 29	5 – 20	0.25
Spironolactone	10 – 35 / Unchanged	98	Unknown
Stavudine	1.0 – 1.4/5.5 – 8	< 1	0.5
Streptokinase	0.6 – 1.5 / Unknown	Unknown	0.02 – .08
Streptomycin	2.5 / 100	35	0.26
Streptozotocin	0.25 / Unknown	Unknown	0.5
Succinylcholine	3 / Unknown	Unknown	Unknown
Sufentanil	2 – 5 / Unchanged	92	2 – 3
Sulbactam	1 / 10 – 21	30	0.25 – 0.5
Sulfamethoxazole	10 / 20 – 50	50	0.28 – 0.38
Sulfinpyrazone	2.2 – 5 / Unchanged	> 95	0.06
Sulfisoxazole	3 – 7 / 6 – 12	85	0.14 – 0.28
Sulindac	8 – 16 / Unchanged	95	Unknown
Sulotroban	0.7 – 3 / 9 – 39	Unknown	Unknown
Tamoxifen	18 / Unknown	> 98	20
Tazobactam	1 / 7	22	0.21
Teicoplanin	33 – 190 / 62 – 230	60 – 90	0.5 – 1.2
Temazepam (Restoril)	4 – 10 / Unknown	96	1.3 – 1.5
Teniposide	6 – 10 / Unknown	99	0.2 – 0.7
Terazosin	9 – 12 / 8 – 12	90 – 94	0.5 – 0.9
Terbutaline	3 / Unknown	15 – 25	0.9 – 1.5
Terfenadine	16 – 23 / Unknown	97	Unknown
Tetracycline	6 – 10 / 57 – 108	55 – 90	> 0.7
Theophylline	4 – 12 / Unchanged	55	0.4 – 0.7
Thiazides	6 – 8 / 12 – 20	40	3.0
Thiopental	3.8 / 6 – 18	72 – 86	1 – 1.5
Ticarcillin	1.2 / 11 – 16	45 – 60	0.14 – 0.21
Ticlopidine	24 – 33 / Unknown	98	Unknown
Timolol	2.7 / 4	60	1.7
Tobramycin	2.5 / 27 – 60	< 5	0.22 – 0.33
Tocainide	14 / 22 – 27	10 – 20	3.2
Tolazamide	4 – 7 / Unknown	94	Unknown
Tolbutamide	4 – 6 / Unchanged	95 – 97	0.1 – 0.15
Tolmetin	1 – 1.5 / Unchanged	> 99	0.1 – 0.14
Topiramate	19 – 23 / 48 – 60	9 – 17	0.6 – 0.8
Topotecan	4 – 6 / Prolonged	Unknown	40
Torsemide	2 – 4 / 4 – 5	97 – 99	0.14 – 0.19
Tranexamic acid	1.5 / Unknown	3	Unknown
Tranylcypromine (Parnat)	1.9 – 3.5 / Unknown	Unknown	Unknown
Triazolam (Halcion)	2 – 4 / Unchanged	85 – 95	Unknown
Trihexyphenidyl	10 / Unknown	Unknown	Unknown
Trimethadione	12 – 24 / Unknown	None	Unknown
Trimethoprim	9 – 13 / 20 – 49	30 – 70	1 – 2.2
Trimetrexate	4 – 22 / Unknown	95	0.6 (10 – 31L/m^2)
Trimipramine (Surmontril)	24 / Unknown	90 – 96	31

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	100%	None	None	None
I	Avoid	NA	NA	Avoid
D,I	50% q 24 h	Dose after dialysis	Unknown	Unknown
D	100%	NA	NA	100%
I	q72 – 96h	1/2 normal dose after dialysis	20 – 40 mg/L day	q24 – 72h
D	50%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	100%	NA	NA	NA
I	q24 – 48h	Dose after dialysis	0.75 – 1.5 g/day	750 mg q12h
I	q24h	1 g after dialysis	1 g/day	q18h
D	Avoid	None	None	100%
I	q12 – 24h	2 g after dialysis	3 g/day	NA
D	100%	None	None	100%
D	10%	Unknown	Unknown	Unknown
D	100%	Unknown	Unknown	100%
D	50%	1/3 dose after dialysis	Dose for Renal Failure	75%
I	q72h	Dose for Renal Failure	Dose for Renal Failure	q48h
D	100%	None	None	NA
D	100%	None	None	100%
D	100%	Unknown	Unknown	100%
D	Avoid	Unknown	Unknown	50%
D	100%	None	None	NA
I	q24h	None	None	q12 – 24h
D	100%	1/2 dose	Unknown	100%
D	Avoid	NA	NA	NA
D	75%	NA	NA	NA
D,I	1 – 2 g q12h	3 g after dialysis	Dose for Renal Failure	1 – 2 g q8h
D	100%	Unknown	Unknown	100%
D	100%	None	None	100%
D,I	20 – 30% q24 – 48h	2/3 normal dose after dialysis	3 – 4 mg/L/day	30 – 70% q12h
D	50%	200 mg	None	100%
D	100%	Unknown	Unknown	Avoid
D	100%	None	None	Avoid
D	100%	None	None	100%
D	25%	Unknown	Unknown	50%
D	25%	Unknown	Unknown	50%
D	100%	None	None	NA
D	10%	Unknown	Unknown	Unknown
D	Unknown	Unknown	Unknown	NA
D	100%	None	None	NA
D	Unknown	Unknown	Unknown	Unknown
I	q12 – 24h	Unknown	Unknown	q8 – 12h
I	q24h	Dose after dialysis	q24h	q18h
D	Unknown: Avoid ?	Unknown	Unknown	Unknown
D	100%	None	None	NA

I.19

Drug	Half-life (hours) Normal/Renal Failure	Protein Binding (Percent)	Volume of Distribution (L/kg)
Tripelennamine	3 – 4.5 / Unknown	Unknown	10
Triprolidine	5 / Unknown	Unknown	Unknown
Tubocurarine	0.5 – 4 / 5.5	30 – 50	0.22 – 0.39
Urokinase	Unknown	Unknown	Unknown
Valacyclovir	3/14	15%	Unknown
Vancomycin	6 – 8 / 200 – 250	10 – 50	0.47 – 1.1
Vecuronium	0.5 – 1.3 / Unchanged	30	0.18 – 0.27
Venlafaxine (Effexor)	4 /6 – 8	27	6 – 7
Verapamil	3 – 7 / 2.4 – 4	83 – 93	3 – 6
Vidarabine	1.5 / Unknown	25	0.7
Vigabatrin	5 – 7 / 13 – 15	None	0.8
Vinblastine	1 – 1.5 / Unknown	75	13 – 40
Vincristine	1 – 2.5 / Unknown	75	5 – 11
Trazodone	6 – 11 / Unknown	89 – 95	1 – 2
Triamcinolone	1.9 – 6 / Unchanged	Unknown	1.4 – 2.1
Triamterene	2 – 12 / 10	40 – 70	2.2 – 3.7
Vinorelbine	20 – 40 / Unknown	15	75
Warfarin	34 – 45 / Unchanged	99	0.15
Zafirlukast	10 / Unchanged	99	Unknown
Zalcitabine	1 – 2 / > 8	< 4	0.54
Zidovudine (AZT)	1.1 – 1.4 / 1.4 – 3	10 – 30	1.4 – 3
Zileuton	2.3 / Unchanged	> 90	2.3

HD are often extrapolated to make dosing recommendations for patients with ARF or those treated with very high flux dialysis. Underestimating drug removal in these circumstances risks ineffective therapy.

Drug Level Monitoring

Plasma drug concentrations guide drug therapy when the relationship between drug levels and efficacy or toxicity is known. These measurements are most important for drugs with a narrow therapeutic range. They may also be useful when drug level-related pharmacological effects are difficult to measure.

If a loading dose is not given, 3 – 4 doses of the drug should be administered before serum levels are measured. This approach ensures that a steady state serum concentration has been established. For some drugs, both maximum and minimum concentrations are relevant. Peak levels are most meaningful when measured after rapid drug distribution has occurred. Conversely, minimum concentrations

Method	Renal Failure Dose	Dose after Hemodialysis	Dose During CAPD	Dose During CRRT
D	Unknown	Unknown	Unknown	NA
D	Unknown	Unknown	Unknown	NA
D	Avoid	Unknown	Unknown	50%
D	Unknown	Unknown	Unknown	Unknown
D,I	0.5 g q24h	Dose after dialysis	Dose for Renal Failure	Unknown
D,I	500 mg q48 – 96h	Dose for Renal Failure	Dose for Renal Failure	500 mg q24 – 48h
D	100%	Unknown	Unknown	100%
D	50%	None	Unknown	NA
D	100%	None	None	100%
D	75%	Infuse after dialysis	Dose for Renal Failure	100%
D	25%	Unknown	Unknown	50%
D	100%	Unknown	Unknown	100%
D	100%	Unknown	Unknown	100%
D	Unknown	Unknown	Unknown	NA
D	100%	Unknown	Unknown	Unknown
I	Avoid	NA	NA	Avoid
D	100%	Unknown	Unknown	100%
D	100%	None	None	None
D	100%	Unknown	Unknown	100%
I	q24h	Unknown	Unknown	Unknown
D,I	100 mg q8h 100%	Dose for Renal Failure None	Dose for Renal Failure Unknown	100 mg q8h 100%

q = every, h = hour, bid = twice daily

are usually measured just before giving the next scheduled dose. A practical schema for drug prescribing in patients with renal impairment is shown in Figure 4.

Patients with renal disease are heterogeneous and their response to drug therapy is variable. Dosage nomograms, drug tables, and computer-assisted dosing recommendations provide guidelines for an initial drug administration in patients with decreased renal function. Individualizing the dose regimen for each patient requires continuing evaluation of the therapeutic response for drug efficacy and toxicity.

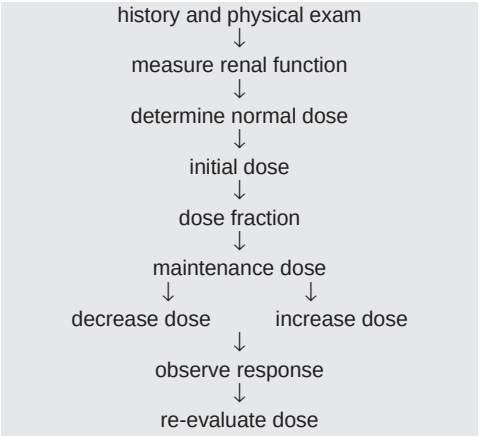

Figure 4. A practical schema for drug dosing in dialysis patients.

References

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Essential (Primary) Hypertension

Friedrich C. Luft

Epidemiology

High blood pressure (hypertension) is the most important risk factor for cardiovascular disease, heart failure, stroke, and the progression of chronic renal disease. Cardiovascular disease is the most common cause of death in the world and is a major cause of morbidity and mortality worldwide [1]. The importance of treating hypertension to prevent cardiovascular disorders was long neglected by physicians; however, this picture is changing, and the number of hypertensive patients who are undetected, or detected but not treated, is now declining. Nevertheless, considerable numbers of patients treated for hypertension have inadequately controlled blood pressure values. Numerous studies have examined the epidemiology of hypertension and its negative impact worldwide. While blood pressure increases with age in both sexes, women appear relatively protected from this increase until menopause, after which their blood pressures increase at an accelerated rate. The age-related blood pressure increase is accelerated in certain groups. For instance, in black persons living in the United States, blood pressure values are higher than those of whites at every age. The risk for developing a stroke or a myocardial infarction is linearly related to the blood pressure level. A recent meta-analysis of the major studies is shown in Figure 1, panels A and B [2]. For both stroke and myocardial infarction, the relationship is linear and begins at blood pressure ranges considered to be normal. This finding has important therapeutic implications. The risk of stroke has been reduced considerably by antihypertensive treatment, so that almost the entire increased stroke risk attributable to hypertension can be eliminated by treatment. This degree of risk reduction has not yet been shown for myocardial infarction; however, the positive influence of treatment on reduced cardiovascular risk is no longer disputed.

Hypertension (except in its extreme malignant phase) is asymptomatic and should therefore be considered a risk factor, rather than a disease. Convincing a patient to take medication with possible side effects for the rest of his life in the hope of prolonging life is not easy. Thus, hypertension must be considered in relationship to other cardiovascular risk factors. The Framingham data clearly illustrate the interrelationships between hypertension, cholesterol, glucose intolerance, cigarette smoking and left ventricular hypertrophy. These five primary risk factors are the most important determinants of cardiovascular risk and appear to operate independently of one another. Other contributing risk factors, such as family history, obesity, hypertriglyceridemia and hyperuricemia exert their influence for the most part through one of the five major risk determinants. Still others, such as lipoprotein (a) concentrations, low HDL/cholesterol, and hyperhomocysteinemia, are currently being identified and evaluated. The threshold at which a patient should be treated is lowered for patients at high risk for cardiovascular disease. High car-

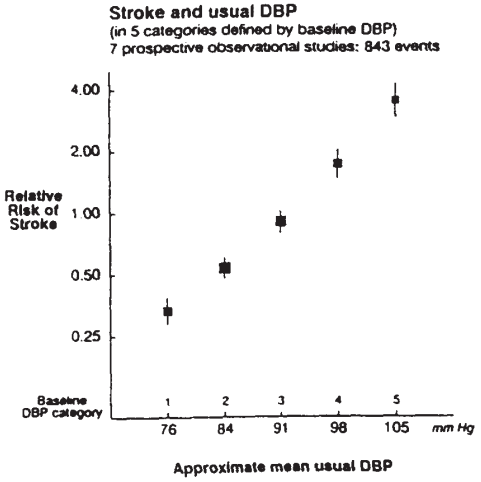

Figure 1a.

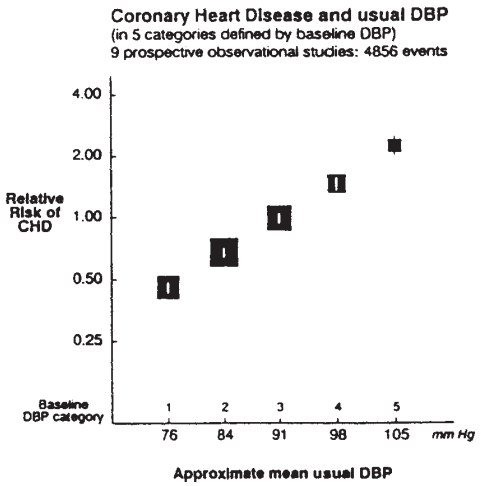

Figure 1. The upper panel shows the relationship between approximate mean diastolic blood pressure and the relative risk of stroke.The lower panel shows the same for relative risk of coronary heart disease. The relationships are linear and are apparent even at the lower end of the blood pressure scale. [MacMahon et al. Lancet 1990; 335: 765-774] with permission.

diovascular risk also calls for a more aggressive approach to treatment.

Epidemiological investigations have also been conducted to examine factors that might promote the development of hypertension in populations. The Intersalt study was performed to examine the influence of body mass index (obesity), salt intake, alcohol ingestion, potassium intake, and protein intake on blood pressure across the world's populations with age. The data were recently reanalyzed [3]. Over 10,000 persons were examined in 50 centers, and 24-hour urine specimens were collected to assess salt, potassium, and protein intake. The study design allowed examination of the effect of these variables on blood pressure increases with advancing age. Obesity has the most pronounced effect on blood pressure. The body mass index is highest in the United States, where currently > 30% of the population can be classified as obese (body mass index > 27.5). Salt intake may influence the age-related blood pressure increase, possibly reflecting a threshold effect of the renin-angiotensin system to altered salt intake. Alcohol and Potassium intake are inversely related to blood pressure. Higher potassium intake increases baroreceptor sensitivity, which decreases short-term blood pressure variability. Blood pressure variability is a cardiovascular risk factor, independent of blood pressure levels. Other studies have shown a convincing influence of potassium intake on stroke incidence, which may be independent of blood pressure. Still other studies suggest that dietary calcium intake is inversely related to blood pressure. This influence may be especially important in pregnancy.

Considerable excitement has been generated by the recent observation that children with low birth weight are likely to be at risk for the development of hypertension and cardiovascular disease as adults. These observations originally stemmed from Great Britain, where excellent birth weight and body length measurements were available from several large hospitals [4]. Several studies from Scandinavia and elsewhere have since confirmed

this observation. These epidemiological studies have strong implications in terms of socioeconomic issues, prenatal health care and nutritional issues, as well as allowing the formulation of additional long-term preventative strategies.

Diagnosis and Clinical Findings

Blood Pressure Measurement

There is no critical blood pressure level that delineates excess risk, since the risk relationships are linear across the range of blood pressure levels (Figure 1). Those blood pressure levels associated with a > 50% increase in mortality are arbitrarily defined as hypertensive. These values are: > 130/90 mm Hg for men younger than 45 years, > 140/95 for men 45 years or older, and > 160/95 mm Hg or greater for all women. Systolic hypertension is present when the systolic blood pressure > 140 mm Hg with diastolic pressure < 90 mm Hg. Borderline hypertension is intermittent elevation of systolic or diastolic pressure exceeding the accepted normal value for the person's age and sex. Criteria for children and adolescents have been established by the National Heart, Lung and Blood Institute of the United States. The following levels are associated with significant risk: > 116/76 mm Hg (3 – 5 years of age), > 122/78 mm Hg (6 – 9 years of age), > 126/82 mm Hg (10 – 12 years of age), and > 142/92 mm Hg (16 – 18 years of age).

Casual blood pressure measurements i.e. standard sphygmo-manometry with an arm cuff using proper technique, is reliable in determining blood pressure, and was used in the above epidemiological studies. Blood pressure should be measured in both arms with the patient comfortably seated. In children and young adults, blood pressure should also be determined in a lower extremity. The arm should be straight with the hand supine. The cuff should be at the level of the heart. If the arm is allowed to hang dependently, or if the cuff is too small, inappropriately high values may be obtained. The cuff width should be greater than two-thirds of the arm's diameter, and the length of the inflatable portion should be greater than two-thirds of the arm's circumference. Systolic pressure is determined at the point at which the sound becomes audible (Korotkoff 1). The diastolic pressure is determined by the point at which sound disappears (Korotkoff 5). Two measurements should be obtained and their values averaged. The patient who on three separate occasions demonstrates a pressure equal to or greater than the above guidelines should be classified as hypertensive. A diastolic pressure of ≥ 90 mm Hg should be confirmed within 3 months. A diastolic pressure of ≥ 105 mm Hg should be confirmed within 2 – 3 weeks.

In older patients with widened pulse pressures, or in patients with severe calcified peripheral vessels (e.g. dialysis patients), the physician must consider the possibility of "pseudohypertension." Pseudohypertension is a falsely elevated blood pressure reading caused by inability of the inflated sphygmomanometer cuff to properly collapse the calcified brachial artery. Palpating the radial artery in the face of an inflated cuff (Osler's sign) is an unreliable physical finding in such patients. Only direct, intra-arterial measurement is adequate to determine the blood pressure of such patients; however, the procedure is tedious and not without morbidity, such as pain and bleeding.

24-hour Ambulatory Blood Pressure Measurement

Technical advances now also permit the measurement of 24-hour ambulatory blood pressure [5]. Such measurements give insight into the expected nocturnal decrease in blood pressure (termed "dipping") and also permit the calculation of the daytime and night-time blood pressure load (values greater than normal during the given period). Blood pressure load is estimated at upper limits 140/90 mm Hg during the daytime and upper limits 120/80 mm Hg at night. The percentage of blood pressure measurements above these values is calculated, and pressure loads > 20% are considered abnormal. Such measurements may be helpful when the diagnosis of hypertension is in doubt, particularly if pharmacological intervention is being considered. Ambulatory 24-hour measurements are also useful to avoid overtreatment. Furthermore, the presence of dipping is quite reliable in excluding secondary causes of hypertension, while the absence of dipping is of little value in suggesting secondary hypertension [6].

White Coat Hypertension

Some persons seem to react to the act of blood pressure measurement in the physician's office with an exaggerated rise in blood pressure [7]. This exaggerated response is termed "white coat" hypertension. Currently, there are no set guidelines for white coat hypertension. However, studies suggest that white coat hypertension is not a harmless phenomenon. Indeed, cardiac changes (decreased ventricular compliance and increased ventricular mass index) have been observed in persons with white coat hypertension, even though the resting blood pressures were not elevated.

History

The history of patients with hypertension should include the identification of other risk factors, namely smoking, hyperlipidemia, diabetes mellitus, family history, and age of hypertension onset. The presence of asthma and chronic lung disease should be noted. The dietary history is important and should cover calorie and electrolyte intake, as well as unusual foods such as licorice. Medications are important, particularly oral contraceptives, steroids, thyroid hormones, anorectics and amphetamine-containing decongestants. Over-the-counter drugs, such as phenylethanolamines, nonsteroidal anti-inflammatory drugs, or materials that contain compounds inhibiting β-OH-steroid dehydrogenase (licorice and certain chewing tobaccos) should be recorded. Symptoms of secondary hypertension should be elicited, such as episodes of headache, perspiration, palpitation, and tachycardia (pheochromocytoma), muscle cramps, weakness, polyuria (primary aldosteronism), peripheral vascular disease, intermittent claudication, previous episodes of pulmonary edema (renovascular hypertension), history of heart murmur and leg claudication (coarctation), family history of renal disease (autosomal dominant polycystic kidney disease) or flank trauma ("Page" kidney). Postural symptoms should be sought, which may indicate baroreceptor reflex failure (autonomic dysfunction or hypokalemia, for example) or hypertension with hypovolemia (pheochromocytoma).

Physical Examination

The physical examination should record height and weight so that the body mass index (weight in kg/[height in m]^2) can be calcu-

lated. Physicians should carefully assess the presence of obesity, and the waist-hip ratio should be measured. They should also evaluate obese hypertensive patients for sleep apnea syndrome, an often overlooked contributor to hypertension. The optic fundi should be evaluated. The thyroid gland deserves attention. In contrast to prevailing opinion, hypothyroidism rather than hyperthyroidism shows a greater association with hypertension. The cardiac examination, including the central and peripheral arteries, should be particularly thorough. Blood pressure should be measured in both arms. Younger patients particularly should have blood pressure measured in the lower extremities, and an infrascapular murmur should be sought. The size of the heart should be estimated and the presence of gallop rhythms recorded. The presence of Cushing's syndrome should be considered. The abdomen must be palpated for polycystic kidneys, and auscultated for systolic and diastolic bruits above the aortic bifurcation. Cutaneous stigmata of Cushing's syndrome and neurofibromatosis should be noted.

Most patients with long-standing hypertension show arteriolar narrowing and increased light reflex (grade I) on funduscopic examination. The veins may be constricted at the site of arteriolar crossing (grade II). Flame-shaped hemorrhages or exudates (ill-defined pale areas) may be present in patients with severe hypertension and are an important finding (grade III). If the optic nerve cannot be distinguished from the surrounding retina or if the optic nerve head is raised (choked), papilledema is likely to be present (grade IV). Such patients should have their mental status (orientation, short-term memory, serial sevens backwards, etc.) carefully evaluated for signs of hypertensive encephalopathy.

Laboratory Evaluation

A complete blood count, urinalysis, electrolytes, serum creatinine, fasting blood sugar, plasma lipids (HDL cholesterol, LDL cholesterol, triglycerides), serum uric acid, and a resting electrocardiogram (ECG) are adequate, provided that the history and physical examination have not revealed other pertinent findings. Patients < 35 years, patients with hypertension of abrupt onset, those with a negative family history, or patients whose hypertension is severe despite treatment warrant further laboratory evaluation. Additional screening procedures for such patients include urine collections for metanephrines (or equivalent), a renal scan before and after captopril (or equivalent such as computed tomography (CT) angiography of the kidney), a chest roentgenogram or other evaluation of to cardiac size, and a stimulated (upright posture) plasma renin activity (PRA) value. Table 1 shows a summary of routine tests for patients with uncomplicated primary (essential) hypertension and patients with suspected secondary hypertension.

An additional consideration in high-risk patients is echocardiography. Patients with moderate to severe hypertension should have a careful assessment of left ventricular hypertrophy, particularly if signs of heart disease are present on physical examination or routine electrocardiogram. Finally, high-risk patients may benefit from the determination of microalbuminuria, which is the first sign of nephropathy in patients with diabetes mellittus and an independent risk factor for heart disease, stroke, and peripheral vascular disease in nondiabetic hypertensive patients [8].

Table 1. Screening Tests for Primary and Secondary Hypertension

Primary hypertension	*Tests*
	Complete blood count Electrolytes Serum creatinine and/or urea concentration Urinalysis, consider microalbuminuria
Special	Optional tests Electrocardiogram 24 h ambulatory blood pressure Echocardiogram
Secondary hypertension	*Tests*
Coarctation	Chest roentgenogram
Cushing's syndrome	Plasma cortisol after dexamethasone suppression
Pheochromocytoma	Urinary vanillylmandelic acid, metanephrines clonidine suppression test
Primary aldosteronism	Serum electrolytes, PRA and Aldosterone with upright posture, PRA/Aldosterone ratio
Renovascular hypertension	Renal scan before and after captopril Renal artery duplex Doppler studies Renal angiography

Pathogenesis of Hypertension

Genetics of Hypertension

Essential (Primary) Hypertension

The familial predisposition to hypertension and its sequelae was observed early in sibling pair, family and monozygotic and dizygotic twin studies. Early investigators concluded that hypertension was inherited as a simple, autosomal dominant trait, suggesting a monogenic defect. In the 1950s, Pickering and coinvestigators convincingly showed that primary hypertension was not inherited in an autosomal dominant, but rather was a complex genetic condition in which 5 – 20 or more genes might be involved. However, unusual forms of inherited hypertension exist in which the hypertension is indeed inherited as a simple monogenic trait. Modern molecular techniques have allowed identification of the gene loci and the cloning of several such hypertension genes. General physicians should be aware of such syndromes; they may be more

common than appreciated and have contributed much to our understanding of blood pressure regulation.

The genetics of primary hypertension has generated great interest. Association and linkage studies have identified susceptibility gene loci. Examples include mutations in the angiotensinogen gene (substitution for methionine by threonine, M235T) and mutations in the catecholamine beta receptor gene. An insertion/deletion mutation in the angiotensin converting enzyme (ACE) gene, which has a substantial effect on ACE plasma levels, has been associated not with hypertension, but rather with the propensity to develop cardiac hypertrophy. Recently, the locus for adducin, a cytoskeletal protein, was linked to hypertension in salt-sensitive individuals.

Rare Genetic Causes of Hypertension

Glucocorticoid remediable aldosteronism (GRA) resembles primary aldosteronism. The mode of inheritance is autosomal dominant, which means that about half the family members are affected, men and women are both involved, and father-to-son transmission occurs. Patients commonly have hypokalemia. The stimulated PRA (upright posture) is low, while the aldosterone values in plasma and urine are elevated. There is no lateralization (adrenal vein aldosterone concentrations are not different), and no tumor is seen on CT or magnetic resonance imaging (MRI). In affected persons, 5 mg prednisone daily relieves the hypertension, suggesting a pathogenic role for adrenocorticotropic hormone (ACTH). The hypertension responds to both thiazide diuretics and to spironolactone, suggesting volume expansion and involvement of the mineralocorticoid receptor. Suspected individuals can have their urine tested for the abnormal steroid products 18 oxo-cortisol and 18 OH-cortisol. Patients have an abnormal chimeric gene located between the genes for 18 β-hydroxylase and aldosterone synthase, containing the promoter region for 18 β-hydroxylase and the structural portion of aldosterone synthase. The gene is expressed in the zona fasciculata, where its product metabolizes cortisol further to aldosterone and the abnormal steroid products. Prednisone 5 mg/day suppresses ACTH, thereby shutting off the chimeric gene. The disease may be diagnosed on the basis of clinical features and with a molecular genetic test. Since the availability of testing, hundreds of families have been found with this disease [9].

Liddle's syndrome is a similar autosomal dominant form of hypertension. These patients also may have hypokalemia; they exhibit a decrease in blood pressure with thiazide, amiloride or triamterene but not spironolactone treatment. Stimulated (upright posture) PRA is low in these patients, however the aldosterone values are also low and abnormal steroids are not found in the urine. Prednisone 5 mg/day makes the disease worse rather than better. Molecular techniques have identified a mutation in genes responsible for the β and γ subunits of the amiloride-sensitive epithelial sodium channel, which is responsible for sodium reabsorption in the distal portion of the distal tubule and collecting duct. Thus, the channel is abnormally active (open state) and sodium (with chloride) is inappropriately reabsorbed, resulting in volume expansion and low-renin hypertension. This defect is probably rare, nevertheless Liddle's disease could account for a portion of patients currently classified as having "low-renin" primary hypertension [9].

Apparent mineralocorticoid excess (AME) is a rare autosomal recessive disease. Affected persons have low stimulated PRA and low

aldosterone concentrations and superficially resemble patients with Liddle's syndrome. However, their blood pressure decreases with both thiazide diuretics and spironolactone, implicating the mineralocorticoid receptor. These characteristics are similar to those observed with licorice gluttony, a rare form of diet-induced secondary hypertension. Licorice contains a substance (glycyrrhizic acid) that interferes with the enzyme 11 β-OH steroid dehydrogenase, responsible for converting cortisol to cortisone in the renal distal tubule. Cortisol has the same affinity for the mineralocorticoid receptor as aldosterone. If the enzyme 11 β-OH steroid dehydrogenase does not function properly, the mineralocorticoid receptor can be inappropriately occupied by cortisol, resulting in a low renin, salt retention form of hypertension. In AME, mutations in the gene responsible for the production of 11 β-OH steroid dehydrogenase have been identified, resulting in a defective gene product. Identification of this disease and elucidation of the syndrome induced by licorice gluttony have drawn attention to this important regulatory system. Numerous plant products contain substances that may inhibit this enzyme, thereby promoting the development of low renin hypertension.

Autosomal dominant hypertension with brachydactyly is an autosomal dominant, monogenic form of hypertension that closely resembles essential hypertension, in that the hypertension is not salt sensitive and the renin-angiotensin axis is normal. A large affected family was found in northeastern Turkey and several affected families in the United States have subsequently been found. Affected family members also have brachydactyly. The responsible gene is not yet cloned, so the mechanisms causing the hypertension have not been elucidated. However, a linkage analysis isolated the gene locus to the short arm of chromosome 12. It is possible that the responsible gene could be relevant to patients with primary hypertension [10].

Autosomal dominant forms of pheochromocytoma exist. Patients with pheochromocytoma should be considered as possibly having one of these diseases. Neurofibromatosis may exhibit bilateral pheochromocytomas. Not all patients with neurofibromatosis have prominent cutaneous neurofibromas, a positive family history, or mental retardation. The skin should be examined carefully for tags, cafe au lait spots and axillary freckling. Von Hippel-Lindau disease (vHL) patients generally have ophthalmologic findings and signs of cerebellar disease. MRI is the diagnostic procedure of choice. Multiple endocrine adenomatosis type II (MEN II) patients have medullary thyroid carcinoma with elevated calcitonin levels, islet cell tumors, parathyroid hyperplasia and a propensity for pheochromocytoma. The pentagastrin test is helpful in making the diagnosis.

Genetic renal diseases may present with hypertension. Patients with autosomal dominant polycystic kidney disease (ADPKD) are invariably hypertensive. Patients with Alport's disease also frequently have hypertension. Family history, physical examination (auditory and ophthalmologic in the case of Alport's disease), simple renal function tests (urinalysis, protein excretion and creatinine clearance), and renal ultrasound are generally sufficient for the diagnosis. Thin membrane disease appears to be familial. This condition features premature glomerular obsolescence and hypertension.

Pathogenic Mechanisms

Blood pressure is determined by the blood flow (cardiac output) and the peripheral vascular resistance. The pathogenesis of primary

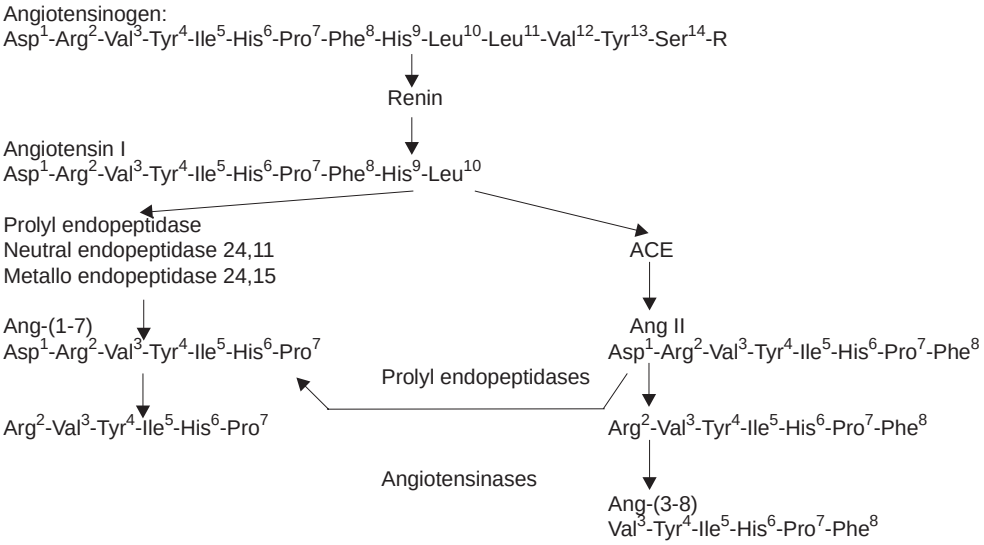

Figure 2. An abbreviated view of the renin-angiotensinogen system.

hypertension involves a series of feedback loops and regulatory systems. These regulatory systems are all interrelated in a cybernetic framework. Disturbances in any system or minor perturbations of several systems can increase blood pressure. Concomitant genetic modifications of several systems probably combine to produce primary hypertension in most cases.

Short-term Blood Pressure Regulation

Changes in blood pressure are sensed by baroreceptors located primarily in the great vessels, especially the aortic arch and the carotid sinus. These receptors relay information to the central nervous system via the vagus and glossopharyngeal nerves. When the blood pressure is low, sympathetic output produces vasoconstriction and a reflex increase in heart rate, as well as secretion of various agents to restore homeostasis. When the blood pressure is high, sympathetic tone is reduced and the heart rate reflexively decreased through parasympathetically-mediated mechanisms. In patients with primary or secondary hypertension, the baroreceptor mechanisms are altered, or "reset," and their sensitivity to a given pressure level decreased.

The Renin-angiotensin System

The renin-angiotensin system a fundamental system of blood pressure and blood volume regulation, is illustrated in Figure 2. Renin is a proteolytic enzyme produced by modified afferent arteriolar smooth muscle cells in the juxtaglomerular apparatus of the kidney. Its release can be stimulated by a local baroreflex mechanism within the kidney involving stretch receptors, by increased renal sympathetic tone, and by altered salt delivery at the macula densa of the distal tubule. Once

released into the circulation, renin acts on the α-globulin angiotensinogen produced by the liver. Renin cleaves off the decapeptide angiotensin (Ang) I. This decapeptide, which has no physiological effects, is cleaved by the ACE primarily in the pulmonary circulation to Ang II, a powerful vasoconstrictor, salt-retaining compound and potential growth factor, which in turn also stimulates aldosterone release from the zona glomerulosa of the adrenal cortex. This biochemical cascade is termed the renin-angiotensin system. Ang II is subsequently degraded to other fragments, Ang (2 – 8), Ang (1 – 7) and Ang (3 – 8). These fragments also have biological activity, especially Ang (1 – 7), which has influences opposite to those of Ang II. Ang (1 – 7) can also be produced directly from Ang I. The renin-angioensin system is extremely complex. Its components are present within the brain, where they regulate salt appetite, drinking behavior, and regulation of autonomic tone. Ang II is generated within the vascular wall of peripheral arterioles and within the heart. Angiotensinogen may be cleaved by enzymes other than renin, and Ang II may be generated by enzymes other than ACE. The importance of these alternative pathways in blood pressure regulation and primary hypertension is imperfectly defined. The renin-angiotensin system is undoubtedly important in primary hypertension, as the recently identified M235T substitution in the angiotensinogen gene suggests.

Primary hypertension can be classified in terms of plasma renin responses to dietary salt intake. Hypertensive patients can be categorized as having low renin, normal renin, and high renin hypertension. This classification has some prognostic implications. For instance, patients with high renin hypertension appear at greater risk to develop myocardial infarction and may benefit less from a salt-restricted diet than patients with normal renin or low renin hypertension. However, many specialized centers have elected not to routinely classify patients with primary hypertension in terms of renin levels, because the therapeutic implications of such classifications are not sufficiently clear. Patient renin levels may be determined in 3 ways: a low salt diet for approximately a week followed by a 24-hour urine sodium excretion compared to the PRA (in the seated position); a volume expansion-contraction protocol (2 L intravenous saline over 4 h on one day, followed by a 10 mmol sodium diet and 40 mg furosemide given 3 time on the second day); or measuring PRA before and after captopril 25 mg. This test is termed the “captopril test” and has been advocated by some groups to identify high renin patients and patients more likely to have renovascular hypertension. Renin and aldosterone responses in various clinical states are given in Table 2. Rarely, renal tumors and cysts can produce renin. The responses in Bartter’s syndrome and diuretic abuse are shown for comparison.

Other Humoral Systems

The kallikrein-kinin system is important to blood pressure regulation. Kallikrein is a renal enzyme that acts on kininogen, a plasma substrate, to release bradykinin. Bradykinin is a vasodilator peptide with important endothelial effects. Bradykinin is degraded to inactive products by ACE. The inhibition of ACE not only blocks Ang II formation, but also raises bradykinin-related effects on blood pressure, renal salt and water excretion, prostaglandin release, and nitric oxide release.

Arginine vasopressin (AVP) is primarily involved in osmoregulation, however the hormone may play a role in volume and blood pressure regulation under special conditions which are not normally associated with hyper-

Table 2. Renin (PRA) and Aldosterone (aldo) Levels in Various Hypertension Syndromes and Bartter's Syndrome

Diagnosis	PRA	ALDO
Renovascular	high	normal to high
Primary ALDO	low	high
Renal tumors and cysts	high	high
Primary hypertension	normal	normal
Low renin hypertension	low	normal
*GRA	low	high
*Liddle's	low	low
*AME	low	low
Hypertension with brachydactyly	normal	normal
*Bartter's	high	high
Diuretic abuse	high	high
High salt intake	low	low

*GRA is glucocorticoid remediable aldosteronism. Liddle's syndrome and hypertension with brachydactyly are other autosomal dominant genetic forms of hypertension. AME is apparent mineralocorticoid excess, an autosomal recessive form of hypertension. Bartter's syndrome (hypotension) is caused by mutations in the Na, 2Cl, K transporter in the ascending limb of Henle's loop.

tension, such as shock, hemorrhage, severe heart failure, and liver disease. Nevertheless, AVP, a powerful vasoconstrictor, is important in certain volume-related forms of hypertension, especially in accelerated or "malignant" hypertension. In these forms, competitive AVP antagonists lower blood pressure acutely. AVP is found at various places in the central nervous system, where it may have important regulatory effects.

In the last decade, a series of endogenous natriuretic factors have been identified. Atrial natriuretic peptide (ANP) is produced in special cells within the atria, and released in response to atrial stretch. The peptide inhibits renin and aldosterone release, and vasomotor tone; modulates glomerular filtration rate (GFR); and promotes diuresis and natriuresis. In addition, ANP increases capillary permeability.

The Vascular Endothelium

The identification of potent vascular endothelial-derived vasoactive substances in the past decade has underscored this organ's major role in blood pressure regulation. The most important vasodilator may be the endothelial-derived relaxing factor nitric oxide (NO). Other vasodilators from the endothelium are the vasodilator prostaglandins, such as prostacylcine, and the endothelial-derived hyperpolarizing factor. The endothelium also produces potent vasoconstrictors such as the prostanoid thromboxane and endothelin. Endothelin is the most potent constrictor known and may contribute to increased peripheral vascular resistance in advanced hypertension, where impaired endothelial function is evident. The endothelium, in response to shear stress and a host of circulating factors, modulates underlying vascular smooth muscle cell tone, as well as growth, differentiation, and angiogenesis.

The Kidney in Hypertension

Short-term regulators (e.g. the baroreceptor reflex mechanism), intermediate-term regulators (e.g. the renin-angiotensin system and cardiac atrial natriuretic factors), and local regulators (e.g. the endothelial cell mechanisms) directly and indirectly influence the kidneys in terms of pressure-natriuresis relationships [11]. A summary is given in Figure 3. The kidneys are responsible for controlling the volume in the body and thereby control the flow relationships determining arterial pressure. The kidneys excrete all salt and water,

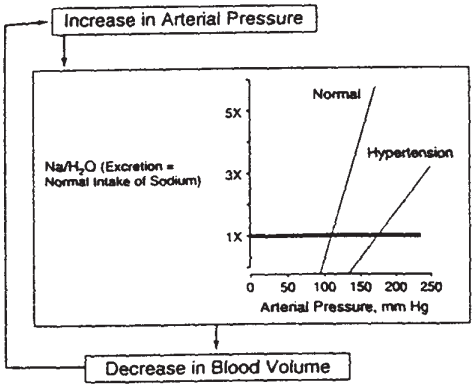

Figure 3. Schematic representation of the pressure-natriuresis relationship for the long-term control of arterial pressure. In normal individuals, any elevation in arterial pressure would be expected to increase sodium and water excretion by pressure natriuresis. Because sodium and water excretion is determined by intake and remains relatively fixed, the increase in sodium and water excretion slowly lowers blood volume sufficiently until arterial pressure returns exactly to control values. If sodium and water are lost from the body, the kidneys retain sodium and water to restore blood pressure to normal. The pressure-natriuresis relationship in hypertension either exhibits a slope reduction or is shifted in a parallel manner toward a higher set point. With reduced slope, the change in blood pressure for any given change in sodium and water intake is greater than normal (sodium sensitivity). With a parallel shift, the relationship between sodium and water intake and blood pressure is changed, however the blood pressure is higher for any given sodium and water intake. [Cowley & Roman. JAMA 1996; 275: 1581 – 1588] with permission.

except that lost through insensible mechanisms. Thus, a relationship between urinary salt and water excretion and the arterial pressure can be defined for every level of arterial pressure or salt and water intake. This relationship, the renal function curve, defines the long-term pressure-regulatory system of the body. In hypertension, the pressure-natriuresis relationship is necessarily shifted to the right. The steepness of the curve defines the relationship between arterial pressure and dietary salt intake and excretion. A relatively flat curve is observed in salt-sensitive hypertension. A steep curve is observed in salt-resistant hypertension. Rarely, e.g. in extreme high-renin hypertension, an inverse relationship may be observed, whereby blood pressure actually decreases with increased salt intake. In physiological experiments, the pressure-natriuresis curve is shifted to the right by the renin-angiotensin-aldosterone system, by catecholamines or sensitivity to catecholamines, AVP, and endothelin. The curve is shifted leftward by ANP, NO, and other vasodilators. Alterations in any and all of these variables, genetic or acquired, can result in primary hypertension.

Secondary Changes Maintaining Hypertension

The longer the duration of hypertension, the greater the tendency of resistance vessels to "adapt" to the elevated blood pressure with media hypertrophy and increased wall-to-lumen ratio (vessel remodeling), which makes the vessels even more susceptible to vasoconstrictors. Thus, the primary (or secondary) mechanism eventually becomes less relevant, because the altered vascular structures themselves serve to perpetuate the condition. Secondary changes also occur in the kidney. Even before clinically evident nephrosclerosis develops, renal blood flow (RBF) declines and renal vascular resistance increases. As a consequence, the salt-excreting capacity of the kidney further decreases , making the hypertension more volume dependent over time. This is the reason that low-renin hypertension is predominant in long-standing hypertension and in older patients. In addition, compliance of large vessels including the aorta declines, impairing the *windkessel* function of the aorta, leading to further increase of systolic blood pressure.

Management

Nonpharmacological Approaches

Multiple Risk Reduction

The purpose of hypertension treatment is to reduce stroke and cardiovascular risk. Thus, hypertension treatment must necessarily consider other risk factors. A person's genetic makeup, age and gender cannot be changed. Volitional risk factors must therefore be addressed. The most important of these is smoking, which constitutes the single leading cardiovascular risk factor. Numerous approaches have been advocated; nicotine-containing gum and patches to wean the addicted patient from smoking have been shown to be effective in randomized trials. The nicotine content of these aids does not influence cardiovascular risk, and patients with preexisting heart disease can use them safely.

The evidence associating cholesterol with heart disease is overwhelming, and several secondary and primary prevention trials have clearly shown that lowering cholesterol lowers cardiac events and mortality. Any dietary approach for hypertension should simultaneously consider cholesterol intake. In the Scandinavian simvastatin trial, stroke also occurred less frequently in the treatment group than in the control group. The value of lowering cholesterol by medication can be estimated from the Sheffield risk tables, which consider age, gender, cigarette smoking, hypertension, diabetes mellitus, and left ventricular hypertrophy on ECG [12].

Diabetes mellitus (DM) is a leading risk factor for stroke and heart disease, and currently half the dialysis patients in the United States and Europe have DM as their primary diagnosis. The incidence of diabetes mellitus is increasing incrementally in all industrialized nations. A fasting blood sugar of 7 mmol/L (125 mg/dL) or a glycosylated hemoglobin level > 7% are sufficient for the diagnosis. Hyperglycemia in diabetic patients must be controlled by diet or medication and control of body mass index is crucial [13].

Weight Control

Weight control is the most important nonpharmacological approach to lower blood pressure [14]. Randomized, controlled trials have documented that weight loss lowers blood pressure. The reduction in blood pressure occurs with the loss of the first few kilograms. The mechanism by which obesity raises blood pressure is not known for certain; however, increased cardiac output and increased sympathetic tone appear to be important. In studies examining various nonpharmacological interventions simultaneously, weight loss was superior to any manipulation of electrolyte intake. The reduction in mean blood pressure to be expected is in the range of 5 – 8 mm Hg. Weight loss is also the most important nonpharmacological approach to DM and has a beneficial influence on cholesterol. The obesity epidemic warrants new novel approaches to weight loss. The discovery of genes responsible for appetite such as leptin will hopefully open new therapeutic options in the future. Currently, no weight loss program has been shown to be consistently successful in the long term, and individual approaches should be attempted. Crash diets, fad diets, complete fasts, and other unbalanced diets should be avoided, because they are generally effective only in the short term. There is good evidence that weight loss with subsequent weight gain is worse than doing nothing at all, making a change in lifestyle necessary to maintain weight reduction.

Aerobic Exercise

Aerobic exercise alone will lower blood pressure if performed approximately 2 times 30 minutes weekly, provided that the intensity provides 70 – 80% of the maximal work load. Such a load will necessarily increase the aerobic capacity. Several specific benefits can be attributed to exercise: patients with severe hypertension on multiple drug regimens can experience regression of left ventricular hypertrophy after regular aerobic exercise that increases aerobic capacity, drug dosage can be reduced in some patients, and improved health consciousness and body image may reinforce lifestyle changes such as smoking cessation.

Reduction of Alcohol Intake

A high alcohol intake (> 30 g ethanol/day) increases blood pressure. In patients whose blood pressure suddenly becomes difficult to control, the possibility of increased alcohol intake should always be considered. Cleverly designed randomized controlled studies have shown that alcohol can increase blood pressure chronically and that lowering alcohol intake can reduce blood pressure. Patients should be encouraged to curtail their alcohol intake to the equivalent of no more than 2 glasses of wine or beer per day.

Reduction of Salt Intake

Randomized, prospective trials have shown that by reducing salt intake, mean arterial blood pressure may be decreased by 5 – 8 mm Hg. Not all patients exhibit a decrease in blood pressure; patients may be divided into salt-sensitive and salt-resistant individuals. The theoretical possibility that salt-resistant persons might exhibit an increase in blood pressure after lowering their salt intake has not been convincingly demonstrated. Thus, all hypertensive patients should be encouraged to reduce their dietary salt intake to < 100 mmol sodium (2.5 g sodium or 5 g table salt) per day. Sodium ingested in the form of other nonchloride salts, such as sodium bicarbonate in mineral water and baking powder has not been shown to increase blood pressure. Ninety-eight percent of sodium is ingested as the chloride salt. Less than one-third of the daily intake is ingested as salt added to the food in cooking or from the salt shaker. The bulk of dietary salt is present in prepared packaged foods. Thus, persons wishing to decrease their salt intake must check food labels accordingly.

Potassium Intake

Increased potassium intake may lower blood pressure in some individuals and decrease the risk of stroke independent of blood pressure-lowering effects. Improved short-term blood pressure regulation and a saluretic effect might mediate these beneficial effects. Because potassium is present in fruits and vegetables, an increase in folic acid can also be expected, which would have the added desirable effect of lowering homocysteine levels. High homocysteine levels have been convincingly associated with increased cardiovascular risk.

Calcium Intake

Increased calcium intake decreases the propensity to develop preeclampsia in pregnant women and may also decrease blood pressure in some hypertensive individuals, in addition to its reduction of osteoporosis risk. Lowering

the dietary salt intake decreases the daily urinary calcium excretion, which may also help maintain calcium homeostasis.

The United States Joint National Committee (JNC) has listed potential benefits of increasing dietary potassium to 3000 mg/day, calcium to 800 – 1000 mg/day, and magnesium to 350 – 400 mg/day, and recommends use of these electrolytes as an effective pharmacological strategy. However, the JNC does not recommend electrolyte supplements unless patients are unable to maintain these levels of intake in their diets.

In summary, the hypertensive patient will benefit from a low calorie, low fat, low salt, high potassium, high calcium diet and an active lifestyle. Such a diet will necessarily be rich in complex carbohydrates as provided by ample amounts of fruits and vegetables. A brief review of nonpharmacological approaches is shown in Table 3. Although nonpharmacological measures have limited value for the treatment of hypertension if applied alone, they may greatly reduce the amount of medication required and even serve as a preventative measure.

Table 3. Life-style Modifications to Lower Blood Pressure, Decrease Cardiovascular Risk, Decrease Medication Requirements, and Possibly Avoid Hypertension*

– STOP smoking!
– Lose weight; desired BMI is 24
– Perform aerobic exercise, preferably daily. Brisk walking 30 – 45 min/day is better than "occasional" jogging
– Limit alcohol intake to 30 g ethanol/day (2 beers, 2 glasses of wine, 1 whiskey-containing drink)
– Reduce salt intake to < 2.5 g (100 mmol) sodium or < 5 g salt daily.
– Increase intake of (fresh) fruits and vegetables, improve potassium, magnesium, and calcium intake
– Modify diet further to consider other risk factors, decrease cholesterol and saturated fat intake

*In accordance with the fifth report of the Joint National Committee and the recommendations of the German Antihypertension League.

Antihypertensive Medications

Four large clinical trials, the Australian Management Committee study, the Oslo study, the Hypertension Detection and Follow-up program, and the Medical Research Council study, showed that patients whose diastolic blood pressure ranged from 90 – 104 mm Hg benefit from drug treatment. Stroke, aortic dissection, heart failure, and cardiac hypertrophy occurred less frequently in treated patients than in control subjects and 2 of the studies showed a reduction in mortality. Elderly patients also benefit from antihypertensive treatment. The Medical Research Council study and the Scandinavian STOP Hypertension study both demonstrated that stroke can be sharply curtailed in the elderly. One of the studies showed a reduction in cardiovascular events, as well as improved mortality. Systolic hypertension is also worth treating. The Systolic Hypertension in Elderly Patients (SHEP) study documented that controlling systolic hypertension reduces stroke and cardiovascular events.

Thus, clinical trials suggest that patients with diastolic blood pressures of 105 mm Hg or greater should be treated aggressively. Patients with blood pressures between 90 – 104 mm Hg can benefit from treatment, as do patients with isolated systolic hypertension. Finally, advancing age should be viewed as an opportunity rather than an impediment for treatment. The level to which blood pressure should be reduced for the greatest risk-reduction benefit is not known. A study currently in

progress is addressing the question of whether diastolic pressures of 90, 85, or 80 mm Hg should be the goal.

Diuretics

Diuretics have been employed in every medication outcomes trial to date. They are proven to reduce stroke and improve cardiovascular risk in hypertensive patients. The most recent (1997) recommendation of JNC stated that diuretics should be considered in the initial treatment of hypertension, unless specifically contraindicated [15]. Such is seldom the case. Significant hypokalemia is unlikely if the diuretic dose is maintained at a low level, and hydrochlorothiazide 25 mg daily is usually sufficient to treat hypertension. Thiazides may be combined with a potassium-sparing diuretic such as amiloride, triamterene, or spironolactone. Hypokalemia should be avoided since it may induce ventricular irritability. Thiazide diuretics may lead to glucose intolerance and increased uric acid serum concentrations. Both are unlikely at the suggested dosage. Hypercalcemia rarely occurs with thiazide diuretics and, if present, suggests hyperparathyroidism. Because thiazides decrease urinary calcium excretion, they are ideal for the treatment of patients with kidney stones, who have a higher incidence of hypertension than the general population, as well as for the treatment of hypertensive osteoporosis patients. Thiazides may increase LDL cholesterol and triglyceride levels, however, the HDL cholesterol level and the ratio of total cholesterol to HDL cholesterol remain unchanged. The changes appear transient and their contribution to cardiovascular risk is unknown [16]. Thiazide diuretics have been shown to be more effective than furosemide in lowering blood pressure in several prospective studies, even when furosemide is given twice daily. Thus, there is no reason to treat hypertensive patients with loop diuretics unless they have reduced renal function (serum creatinine > 3 mg/dl) or salt retention. Potassium-sparing diuretics are less potent than hydrochlorothiazide and should not be given alone, together with ACE inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs), since hyperkalemia may ensue. Diuretics are inexpensive, given once daily, and can conveniently be combined with other medications – all features contributing to compliance. Subjective side effects include sexual dysfunction, which in one study occurred even more frequently than during beta blocker therapy.

Beta Blockers

Beta blockers were also included in all medication outcomes trials to date. They are also proven to reduce stroke and to improve cardiovascular risk in hypertensive patients. The JNC concluded that like diuretics, beta blockers should be considered in the initial treatment of hypertension, unless specifically contraindicated. Beta blockers have also been shown to reduce mortality after myocardial infarction and recently to reduce cardiovascular mortality after any major surgery in patients at cardiovascular risk. Beta blockers are, along with nitrates, the drug of choice for angina pectoris. Thus, the argument to use beta blockers in the treatment of essential hypertension is compelling. Beta blockers are effective as initial therapy, particularly in young and middle-aged patients, 50 – 75% of whom respond. The response rate for older patients is somewhat lower. Beta blockers also function well combined with other medications. The blood pressure-lowering action of beta blockers is still not entirely clear, however beta blockers reduce cardiac output and

reduce renin release. At higher doses, a renin-independent central nervous system effect is also operative.

Beta blockers have several disadvantages. They are contraindicated in persons with asthma and difficult to use in patients with chronic lung diseases. They diminish aerobic exercise tolerance to some degree, although they do not interfere with the benefits of aerobic exercise. Beta blockers should be used with caution in patients with congestive heart failure, although several recent trials have shown beta blockers to be beneficial in the treatment of congestive heart failure and more studies addressing this issue are under way. Beta blockers should not be given to patients with atrioventricular conduction disturbances and should not be combined with verapamil. Beta blockers may make intermittent claudication worse. They may induce depression and nightmares in some patients. They may make hypoglycemic episodes less noticeable in diabetic patients receiving insulin by blocking the expected tachycardia and diaphoresis. Diabetic patients should be warned accordingly. Beta blockers may increase the ratio of total cholesterol to HDL cholesterol, although the effect on cardiovascular risk is unknown.

Different types of nonselective and selective beta blockers are available from which to choose. Propranolol, nadolol, and timolol are nonselective beta blockers. The latter 2 are long-acting. Atenolol and metoprolol are selective beta blockers, while celiprolol is highly selective. Some beta blockers, such as pindolol, also have an intrinsic sympathomimetic activity, which may obviate the cardioprotective effect offered by beta blockers in coronary heart disease. Labetalol combines both alpha- and beta-blocking properties. This drug is effective in the oral or intravenous treatment of hypertensive emergencies and may be used for the treatment of known or suspected pheochromocytoma. Labetalol is also helpful in the treatment of preeclampsia and related syndromes. Carvedilol is a beta blocker that has some alpha- and calcium channel-blocking activities.

Alpha Blockers

Alpha blockers, such as prazosin, terazosin, and doxazosin block smooth muscle post-synaptic alpha1 receptors. Urapidil is an alpha blocker that also has a central mode of action, and may be given parenterally. Alpha blockers do not usually induce a reflex increase in cardiac output and renin release, and may be combined with other drugs. Alpha blockers are generally well tolerated. Rarely, a patient may experience sudden syncope, usually postural after the first dose of prazosin. The mechanism is unexplained. Physicians frequently begin prazosin treatment with a 1 mg evening dose taken with the patient already supine. Postural hypotension may occur in 2% of patients; special care must be taken in patients with previous syncope and in the elderly. Alpha blockers may be particularly helpful in patients with known or suspected pheochromocytoma and also in patients with Raynaud's phenomenon. Alpha blockers cause at least a short-term reduction in serum lipids of unknown significance. They are associated with retrograde ejaculation in some patients. Alpha blockers are also particularly useful in patients with benign prostatic hypertrophy. In a recent trial alpha blockers were more effective in alleviating this condition than inhibitors of dihydrotestosterone.

Angiotensin-converting Enzyme (ACE) Inhibitors

ACE inhibitors inhibit the production of Ang II, inhibit the degradation of bradykinin,

and increase serum concentrations of Ang (1 – 7). They are very successful in reducing blood pressure. Moreover, ACE inhibitors have revolutionized the treatment of congestive heart failure and increase survival after myocardial infarction, even in patients with good left ventricular function. The short-acting ACE inhibitor captopril was the first of this class available and was given to patients in doses up to 300 mg/day, although such doses are rarely indicated. The recommended starting dose in moderate to severe hypertension is 25 mg 2 – 3 times daily. ACE inhibitors all have characteristic side effects, including cough, upper respiratory congestion, allergy-like symptoms, and dysgeusia. Rarely, angioneurotic edema may occur. Such effects have been attributed to bradykinin. Proteinuria is said to occur in 1% of patients; however, careful investigations of putative ACE inhibitor-induced proteinuria did not convincingly show that the ACE inhibitor was responsible. ACE inhibitors may increase creatinine levels, particularly in patients with a solitary kidney with vascular stenosis. Reversible granulocytopenia was reported with captopril after its introduction, possible related to high doses. ACE inhibitors are contraindicated during pregnancy or in women intending to become pregnant because of teratogenicity. An important side effect of ACE inhibitors is hyperkalemia, particularly in patients with some decrease in renal function (e.g. DM) who are simultaneously receiving a potassium-sparing diuretic, NSAID, beta blockers, and digitalis. This effect is termed secondary hypoaldosteronism and is an expected pharmacological action rather than a side effect.

Certain captopril-related side effects were attributed to the presence of a free sulfhydryl group; other ACE inhibitors have been introduced without this sulfhydryl group. Similar side effects have been observed with enalapril and lisinopril. Additional ACE inhibitors available include benazepril, fosinopril, quinapril, and ramipril. With few exceptions, the indications, dosage range, duration, and side effects of these ACE inhibitors are similar to those outlined above. Fosinopril is eliminated by both the kidneys and liver, and consequently no dosage adjustment is necessary with reduced renal function. Ramipril is the ACE inhibitor with the best documentation regarding blood pressure reduction 24 hours after administration.

Prospective trials in patients with diabetic nephropathy and patients with a variety of renal diseases indicate that ACE inhibitors favorably influence the progression of chronic renal disease. In these trials, patients received their usual antihypertensive agents and were then randomized to either the ACE inhibitor or a placebo tablet. The blood pressure values of the ACE inhibitor-treated patients were slightly lower than in the control group, suggesting that blood pressure lowering is the most important aspect. Impressive data have also been accrued regarding the reduction of proteinuria and microalbuminuria in patients with type II DM. ACE inhibitors are also effective in the regression of ventricular hypertrophy. The action of ACE inhibitors is potentiated by a low-salt diet, thiazide diuretics, and loop diuretics.

Angiotensin Receptor Antagonists and Renin Inhibitors

The renin-angiotensin cascade can be inhibited at various places. Ang II has two major receptors. The AT-1 receptor mediates smooth muscle cell contraction, renal sodium reabsorption, aldosterone release, and central effects of drinking and salt appetite. Effective blockers of the AT-1 receptor have been introduced. These small nonpeptide molecules are well absorbed orally and very well tolerated.

Angiotensin receptor antagonists do not cause angioneurotic edema and have no effect on bradykinin elimination that can cause cough or respiratory symptoms. Thus, the 15% of patients who have difficulty tolerating ACE inhibitors may be effectively treated with angiotensin receptor antagonists. Angiotensin receptor antagonists result in increased PRA and increased production of Ang II. Theoretically, the AT-2 receptor is more likely to be occupied when the AT-1 receptor is blocked. The functions of the AT-2 receptor have not been clarified, however, it may exert an antiproliferative effect on vascular tissue. Two AT_2 receptor blockers, losartan and valsartan, have been introduced into clinical practice. A double-blind prospective trial showed that losartan lowered blood pressure as effectively as enalapril.

Calcium Channel Blockers

Calcium channel blockers work by inhibiting calcium influx via the L-type, voltage-dependent calcium channel on vascular smooth muscle cells. Verapamil is also particularly effective in the cardiac conduction system. As a class, the drugs can be considered arteriolar vasodilators. The claims that calcium channel blockers are specifically helpful in the elderly, black patients, and salt-sensitive hypertension patients have not been backed up by prospective clinical trials.

Nifedipine was the first of the dihydropyridine calcium channel blockers introduced. A short duration of action (only 4 – 6 h) means that it must be given 3 – 4 times daily. Side effects include flushing, headaches, and postural hypotension. Although often used to treat hypertension, short-acting nifedipine was never approved for this indication by the United States Food and Drug Administration. Furthermore, although advocated for the treatment of hypertensive emergencies by some, recent considerations suggest that its use in this clinical setting is not without problems [17]. Longer-acting forms of nifedipine lack these undesirable side effects. Additional long-acting dihydropyridines are now available, including amlodipine, felodipine, isradipine, and nicardipine. The side effects and efficacy seem similar to those of long-acting nifedipine. Both short- and long-acting calcium channel blockers may cause pedal edema. The edema probably results from increased intracapillary pressure from peripheral arteriolar dilatation and is not related to primary renal salt retention.

Diltiazem (a benzothiazepine) and verapamil (a phenylalkylamine) are nondihydropyridine calcium channel blockers. They differ from the dihydropyridines by their chronotropic properties. Verapamil particularly is associated with constipation, and patients should be alerted. Verapamil and diltiazem should be used with extreme caution in patients with conduction abnormalities or on beta blockers.

New types of calcium channel blockers are being introduced that not only inhibit voltage-dependent L-type calcium channels, but also T-type calcium channels. Mibefradil is such a compound, and has a greater affinity for the T-type calcium channel than the L-type calcium channel. Mibefradil dilates both coronary and peripheral arteries, with a slight decrease in heart rate. Nevertheless, mibefradil leads to no decreased inotropic effects. The drug's half life is sufficiently long to permit once daily administration. A placebo-controlled trial in patients with hypertension showed a 15 – 18 mm Hg blood pressure decrease at higher doses compared to a 3 – 5 mm Hg reduction for placebo.

The calcium channel blockers have been used as first-line antihypertensive drugs. They possess excellent blood pressure-lowering ef-

ficacy. Calcium channel blockers have a natriuretic action and are not associated with salt and water retention, making them very popular with physicians. Recently calcium channel blockers, particularly short-acting nifedipine, have come under attack. In retrospective, case-control, observational studies, patients receiving nifedipine, verapamil, and diltiazem experienced increased numbers of adverse cardiovascular events compared to patients not receiving these drugs. Numerous confounding variables played a role in these studies and iron-clad conclusions cannot be drawn. In a prospective trial comparing isradipine to hydrochlorothiazide, adverse cardiovascular events were, if anything, more common ($p=0.07$) in the isradipine group than in the control group. Prospective comparative trials involving calcium channel blockers and ACE inhibitors, neither of which have as yet been shown to reduce morbidity and mortality in patients with hypertension, will hopefully clarify these issues. Finally, the use of short-acting nifedipine in patients with hypertensive urgencies or emergencies has been challenged on the basis of frequent complications, such as acute stroke. The use of nifedipine in this setting should be re-evaluated.

Centrally Acting Agents

Clonidine, moxonidine, methyldopa, and guanabenz act in the central nervous system. Initially, an $alpha_2$-adrenergic agonist action was postulated, but current thinking favors activation of imidazoline receptors. Clonidine can be extremely effective in patients with severe hypertension or renin-dependent disease. It acts by decreasing sympathetic output from the central nervous system. Side effects include dry mouth, drowsiness, delayed alertness, depression, and impotence, and are dose related. A convenient transdermal patch is available. Clonidine has specific usefulness in treating patients with cocaine-related effects, methamphetamine effects, and hyper reactivity associated with withdrawal states. The patch is also very convenient in this therapeutic setting. Anecdotal information suggests that clonidine may also help hypertensive smokers attempting to quit. Methyldopa has been safely and reliably used for decades. The drug has a particular niche in the treatment of hypertension in pregnancy, primarily because of its long track record rather than on the basis of controlled clinical data. Methyldopa may also act by serving as a false neurotransmitter. Centrally-acting agents, particularly Clonidine, have been associated with substantial rebound hypertension if suddenly discontinued. Moxonidine, which binds selectively to imidazole receptors in the rostral ventrolateral medulla, has fewer side effects and less tendency to cause a withdrawal syndrome, although it also should be withdrawn with caution.

Guanethidine and Guanadrel

These drugs deplete catecholamines from nerve endings. The compounds have a wide dose-response range and are not associated with sedation. Side effects include orthostatic hypotension and diarrhea. In today's practice, these drugs are primarily of historic interest.

Reserpine

Reserpine has a long history and was included in the initial controlled trials which indicated that antihypertensive treatment decreases stroke and cardiovascular risk. Reserpine in higher doses may initiate sudden severe depression; it should be administered only to emotionally stable patients who have

been informed. Depression is unusual with doses ≤ 0.25 mg/day. Once-a-day treatment is effective. Reserpine's efficacy and low cost suggest that its world-wide role should be reconsidered.

Vasodilating Agents

Hydralazine and minoxidil are vasodilators that probably work by facilitating potassium entry into vascular smooth muscle cells. Minoxidil is more potent. Both drugs cause reflex tachycardia and renal salt and water retention and should thus be used together with a beta blocker and loop diuretic. Hydralazine may cause a lupus-like syndrome (usually sparing the kidneys) when given at doses > 200 mg/day. Minoxidil causes hair growth, a side effect for which the drug is marketed as a topical agent. Minoxidil is effective in severe refractory hypertension and should be considered in patients requiring three or more drugs to control their blood pressure.

Agents Under Development

Nonpeptide, orally absorbable renin inhibitors have been developed, which may offer a new means to alter the renin-angiotensin system. Remikiren, enalkiren and zankiren are examples. Neutral endopeptidase inhibitors, such as candoxatrilat, candoxatril, and sinoxpidan lower blood pressure by preventing the degradation of atrial natriuretic peptide, resulting in natriuresis and vasodilatation. Endothelin inhibitors are being developed that are capable of blocking the action of endothelin at its specific receptor site. NO inducing compounds, such as L-arginine, could decrease peripheral vascular resistance by promoting NO production. Renomedullary depressor lipids, such as medulipin, are being considered to promote vasodilatation, sympathetic nervous system suppression, and natriuresis. New potassium channel openers, such as pinacidil, cromakalim, and levcromakalim, are being developed to hypopolarize cells, alter calcium flux, and reduce vascular smooth muscle tone.

Choice of Drugs

Surprisingly, the antihypertensive efficiency of all antihypertensive drugs when given singly is similar, decreasing blood pressure by about 8 mm Hg, compared to placebo. This result is probably related to the many different feedback loops controlling blood pressure simultaneously. Interference with any one system results in counter-regulatory mechanisms, which limit the effect of any single agent.

The most recent JNC (1997) recommendation reversed a previous stand and suggested that antihypertensive treatment should commence with diuretics and beta blockers. If necessary, the two drugs could be combined. Cost and documented efficacy of risk reduction stemming from prospective clinical trials played a role in the JNC recommendation. The recommendation is controversial; the International Society of Hypertension and the German Antihypertension League published different recommendations. These expert groups suggested that thiazides, beta blockers, ACE inhibitors, alpha blockers, and calcium channel blockers are all first line agents [18]. Initial treatment could commence with any of these drugs, with addition of a second as needed.

A trial is in progress testing the efficacy of five drug classes in terms of stroke and cardiovascular event reduction. The results of this trial will not be available for several years to come. Thus, initial treatment decisions re-

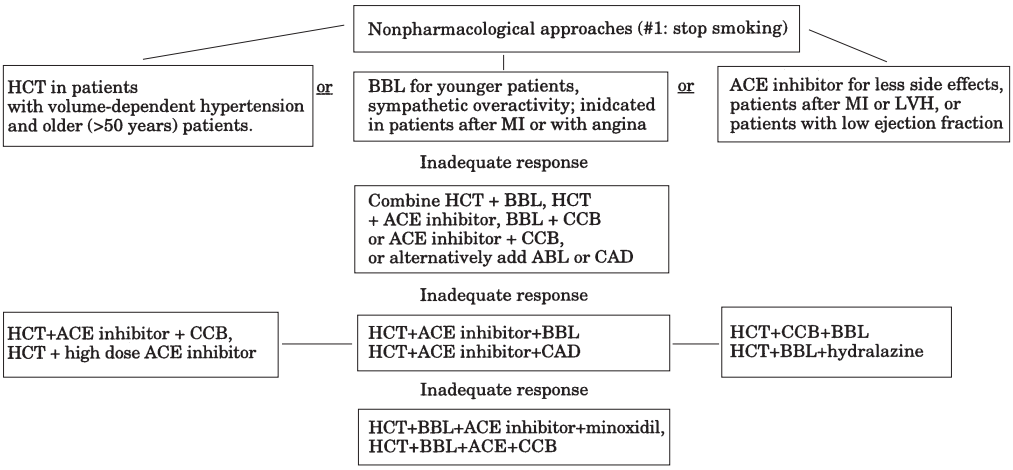

Figure 4. A simplified approach to the treatment of hypertension*. Suggestions are flexible and are intended as examples. HCT = hydrochlorothiazide (or equiv), BBL = beta blocker (combined beta + alpha blocker acceptable), ACE = angiotensin converting enzyme inhibitor, CCB = calcium channel blocker, ABL = alpha$_1$-blocker, CAD = centrally acting drug.

main essentially empirical and are based on blood pressure-lowering effects, a surrogate endpoint, since the primary concern is decreasing the incidence of stroke and cardiovascular disease. In recent years, physicians have frequently chosen to begin treatment with an ACE inhibitor or a calcium channel blocker because of perceived decreased side effects, even though the best "hard end point" data are available for diuretics, beta blockers and reserpine. Diuretics have waned in popularity because of concerns about hypokalemia and their lipid-raising potential. The TOMHS study examined the effects of monotherapy in patients with mild hypertension followed for 4 years, compared to a nonpharmacological intervention [19]. The drugs administered in the trial included an ACE inhibitor (enalapril), beta blocker (acebutolol), diuretic (chlorthalidone), calcium channel blocker (amlodipine), and an alpha blocker (doxazosin). The drugs were more effective than the nonpharmacological intervention; however, the antihypertensive effect was not significantly different among the regimens: about 6 – 8 mm Hg. Side effects were few and not significantly different from placebo. Regression of left ventricular size was monitored echocardiographically in the patients and interestingly, the thiazide diuretic was comparable to the other drugs, in this respect.

A decision tree is suggested in Figure 4. In terms of monotherapy, treatment should begin with a thiazide diuretic or a beta blocker. Young patients with autonomic hyperactivity, patients with angina pectoris, or patients who have had a myocardial infarction should receive a beta blocker. Older patients, or patients with salt-sensitive, volume-dependent hypertension do well with a low dose of hydrochlorothiazide. In patients with reduced ventricular function (even mild heart failure), an ACE inhibitor should be given. Two-drug therapy is best accomplished by combining a thiazide

diuretic with a beta blocker or an ACE inhibitor. A long-acting calcium channel blocker can be conveniently combined with a centrally acting drug or an ACE inhibitor. A dihydropyridine can also be combined with a beta blocker. The combination of a calcium channel blocker with a diuretic is said not to be particularly effective because both exert a natriuretic action; however, the scant controlled data addressing this issue are not convincing. Interestingly, different classes of calcium channel blockers can be combined to achieve an even greater blood pressure-lowering effect.

Severe hypertension may require three or more drugs. A diuretic, high-dose ACE inhibitor, and a calcium channel blocker or beta blocker can be considered. An alpha blocker or a centrally-acting drug may be a valuable addition. If the hypertension is refractory, physicians should not refrain from prescribing minoxidil in combitnation with a beta blocker and a diuretic to avoid reflex tachycardia and salt and water retention.

Several points need to be kept in mind. Compliance to life-long drug therapy is always problematic. A single daily dose has the best chance for success. Even twice daily dosage is questionable. Thus, formulations must be selected that allow for single daily dosing. Requirement for such a formulation is a > 50% "peak to trough" ratio of blood pressure-lowering effect, which means that at least half the maximal potency must be retained after 24 hours. Physicians must ask about side effects. Patients seldom volunteer information about impotence, depression, and nightmares, and may not recognize cough. The young male patient with impotence may simply not take his medicine. The spouses of the patients should be asked about side effects as well, as their answers are often illuminating. The nonpharmacological approaches should be regularly stressed. If hypertension continues or recurs, the physician should consider increased alcohol intake, excessive salt intake, noncompliance, or secondary hypertension. The latter (e.g. renal artery stenosis) occasionally develops superimposed on essential hypertension. Patients should be taught the names of their medicines. They should be able to recognize each tablet, know their dosage schedules, and have these written down and readily available. It is surprising what human beings will ingest without question.

Home blood pressure monitoring by the patients themselves has become popular. Inexpensive sphygmomanometers, or wrist blood pressure measuring devices, are available and the practice of home monitoring is helpful. However, the devices are not all reliable and should be regularly compared to a mercury column sphygmomanometer in the physician's office. Furthermore, blood pressure monitoring can become a fetish and an obsession. As a result, patients frequently juggle their medicines on their own without informing their physicians. Patients must understand that antihypertensive treatment is a life-long, marathon treatment of a risk factor designed to protect against stroke and heart attack. A momentary blood pressure value is of only marginal interest. Finally, patients must be made aware that hypertension, with the exception of malignant hypertension, is asymptomatic. The lay public and many physicians are firmly convinced that hypertension is responsible for headache, dizziness, nose bleeds, flushing, tinnitus, and other perturbations of daily life. A prospective study examining this issue showed no difference in the appearance of such symptoms in hypertensive patients and a normotensive control population.

Last but not least, long-term use of antihypertensive drugs is safe and well tolerated. In a study of 5,485 hypertensive patients, no

deaths attributable to the therapy were reported, fewer than 1% of patients required hospitalization for side effects, and only 9% had side effects sufficiently severe to require a change in pharmacological therapy.

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Hypertension Secondary to Parenchymal Renal Diseases

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Introduction

The association between hypertension and chronic renal disease is well recognized. Hypertension occurs in approximately 80% of patients with end-stage renal disease (ESRD), and renal disease is by far the most common cause of secondary hypertension. Hypertension is an important presenting feature of renal disease and contributes to its progression. A history of long-standing arterial hypertension is associated with an increase in cardiovascular mortality, the leading cause of death in patients receiving maintenance hemodialysis. Although no controlled studies are available on the beneficial effect of antihypertensive therapy in patients on hemodialysis, maintenance of good blood pressure control is of great importance for the long-term survival of these patients. Hypertension is the single most important predictor of coronary artery disease in uremic patients, even more predictive than cigarette smoking or hypertriglyceridemia.

A large number of hypertensive hemodialyzed patients manifest no diurnal variation of blood pressure and absent or reduced nocturnal dipping of blood pressure. This is of particular clinical relevance, as a relationship seems to exist between the absence of nocturnal fall in arterial blood pressure and severity of cardiovascular target organ damage.

Pathogenesis

The pathogenesis of hypertension in renal parenchymal diseases is multifactorial (Table 1). However, the most important factors

Table 1. Factors Implicated in the Pathogenesis of Hypertension in End-stage Renal Disease (ESRD)

1. Sodium and volume excess
2. The renin-angiotensin system
3. The adrenergic system and baroreceptor activity
4. Endothelium-derived vasodepressor substances
5. Endothelium-derived vasoconstrictor substances
6. Erythropoietin use
7. Divalent ions and parathyroid hormone
8. Atrial natriuretic peptide
9. Structural changes in the arteries
10. Preexistent essential hypertension
11. Miscellaneous:
    - Anemia
    - A-V fistula
    - Vasopressin
    - Serotonin
    - Thyroid function
    - Calcitonin gene-related peptide.

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appear to be sodium retention, activation of the renin-angiotensin system, and increased activity of the sympathetic nervous system.

The Role of Sodium and Volume Status

Sodium retention and volume expansion occur in a large number of patients with renal functional impairment and play a major role in the genesis and maintenance of hypertension in these patients. Restriction of dietary sodium intake and removal of excessive fluids with dialysis may result in improvement or normalization of blood pressure in approximately 50 – 60% of patients.

The mechanisms by which sodium excess may lead to arterial hypertension in patients with renal parenchymal diseases are complex. According to Guyton's hypothesis [1], initially sodium excess leads to volume expansion and to increased cardiac output. Eventually, this is followed by an increase in total peripheral vascular resistance and by normalization of cardiac output. In patients with renal failure and normal blood pressure, the increase in cardiac output is fully compensated by a decrease in peripheral vascular resistance. This compensatory adaptation does not occur in patients who develop hypertension. The increase in peripheral vascular resistance may be due to inappropriately elevated levels of angiotensin II in relation to the body fluids and volume status. Alternatively, sodium overload may increase the secretion of digitalis-like inhibitors of the Na-K-ATPase in vascular smooth muscle cells, resulting in hypertension. Boero et al. [2] found lower erythrocyte Na-K-ATPase activity in hypertensive than in normotensive uremic patients. In the hypertensive group, an inverse correlation was present between Na-K-ATPase activity and peripheral vascular resistance. Inhibition of the Na-K-ATPase pump leads to increased cytosolic sodium and calcium concentrations, enhanced vascular tone, and enhanced vascular responsiveness to vasoconstrictors. The increase in intracellular sodium may also cause swelling of arteriolar walls and narrowing of the lumen of arterioles, which may contribute to the increased peripheral vascular resistance. The inhibition of the Na-K-ATPase pump could also result in activation of the sympathetic nervous system.

The Role of the Renin-angiotensin System

The role of the renin-angiotensin system in the pathogenesis of hypertension in patients with chronic renal failure has long been well recognized. This is supported by several observations. First, in these patients an abnormal relationship frequently exists between exchangeable sodium or blood volume and plasma renin-activity (PRA), and between PRA and blood pressure. Second, in most of these patients blood pressure can be effectively reduced by the administration of inhibitors of the renin-angiotensin system, such as angiotensin (Ang) converting enzyme (ACE) inhibitors or angiotensin II antagonists. Finally, bilateral nephrectomy almost always normalizes even the most severe forms of hypertension in patients with renal failure.

The Role of the Sympathetic Nervous System

The kidney is a sensory organ richly innervated with sensory and afferent nerves of two types:

– renal baroreceptors which increase their firing in response to changes in renal perfusion and intrarenal pressure;
– renal chemoreceptors, which are stimulated by ischemic metabolites or uremic toxins [3, 4].

The activation of these chemosensitive receptors and renal afferent nerves may establish connections with integrative nuclei of the sympathetic nervous system in the brain [5]. Stimulation of these afferent nerves by ischemic metabolites, such as adenosine, or by urea, evokes a reflex increase in sympathetic nerve activity and blood pressure [6].

In patients with chronic renal failure, plasma norepinephrine (NE) levels are frequently high. Direct microelectrode recordings of postganglionic sympathetic action potentials in peroneal nerves have shown greater sympathetic nerve discharge in dialysis patients with their native kidneys than in patients with bilateral nephrectomy or control subjects. These findings support the notion that increased afferent nervous inputs from the kidney to the central nervous system may play a role in the pathogenesis of hypertension in uremic patients.

The strongest evidence yet supporting a role of the sympathetic nervous system in the pathogenesis of hypertension in chronic renal failure (CRF) derives from animal experiments. The turnover rate of NE was greater in the posterior hypothalamic (PH) nuclei and in the locus coeruleus of rats with chronic renal failure than in control rats. Chemical destruction of the PH by micro-injection of a neurotoxin, 6-OH-dopamine, reduced blood pressure almost to normal in CRF animals [7]. Bilateral dorsal rhizotomy (T10 to L2) prevented the development of hypertension and the increase in NE turnover rate in the PH and in the locus coeruleus of CRF rats [8]. This suggests that renal afferent impulses from a diseased kidney activate areas of the brain involved in the neuroadrenergic regulation of blood pressure and contribute to the development of hypertension in CRF rats.

The Role of Endothelial-derived Vasodilator Factors

The endothelial cells serve as the interface between the circulating blood and vascular smooth muscle cells and play a crucial role in regulating regional blood flow and vascular resistance. The endothelium is the major source of prostacyclin, which increases cyclic adenosine monophosphate (cAMP) in the vascular smooth muscle cells, leading to vasodilatation. The acetylcholine-induced arterial relaxation is endothelial dependent and is caused by the generation of a diffusible and transferable substance that relaxes smooth muscle cells. This substance is nitric oxide (NO). Prostacyclin and NO potentiate each other's vascular and platelet anti-aggregating effects even at subthreshold concentrations.

NO is formed in the vascular endothelium by NO synthase from the amino acid L-arginine. Several forms of NO synthase have been identified. The first is a constitutive, cytosolic Ca^{2+}/calmodulin-dependent form that releases NO for short periods in response to receptor or physical stimulation. The second is an inducible form that is Ca^{2+}-independent and can be activated by tetrahydrobiopterin and cytokines. Among other NO synthases is the neuronal form, which exerts a modulatory action on the activity of the sympathetic nervous system. Chronic inhibition of NO synthesis by L-Nitro-Arginine-Methyl-Ester (L-NAME) causes a sustained elevation of blood pressure and marked renal vasoconstriction, a fall in glomerular filtration rate and a rise in filtration fraction, plasma

renin levels, and SNS activity [9, 10]. Widespread arteriolar narrowing, focal arteriolar obliteration, and segmental fibrinoid necrosis of the glomeruli may also occur [11]. Vallance et al. [12] have shown that NO synthesis can be inhibited both in vitro and in vivo by an endogenous compound, N^GN^G-dimethylarginine (asymmetrical dimethylarginine, ADMA). They found higher plasma levels of ADMA in uremic patients on chronic hemodialysis and suggested that hypertension in the uremic patient may be due to NO synthesis inhibition caused by accumulation of this endogenous inhibitor.

We have evaluated the effects of L-arginine and L-NAME on blood pressure and SNS activity in Sprague Dawley 5/6 nephrectomized (CRF) or sham operated rats. NE turnover rate was increased in the posterior hypothalamic nuclei, locus coeruleus, paraventricular nuclei, and rostral ventral medulla of CRF compared to control rats. NO synthase (NOS) messenger RNA (mRNA) gene expression and NO_2/NO_3 content were also increased in the same brain nuclei. L-NAME increased blood pressure and NE turnover rate in the brain of control and CRF rats. In CRF rats, a significant relationship was present between the percent increment in NO synthase mRNA gene expression related to the renal failure, and the percent increase in norepinephrine turnover rate caused by L-NAME. This suggests that endogenous NO partially inhibits the activity of the SNS in brain nuclei involved in the neurogenic regulation of blood pressure, and this inhibition is enhanced in CRF rats [13].

The Role of Endothelium-derived Vasoconstrictor Factors

The endothelium releases very potent vasoconstrictors, such as endothelin (ET) [14], Prostaglandin H_2, and epidermal growth factor. These vasoactive peptides may play a role in disease states such as hypertension.

Compelling evidence that ET may play a role in the pathophysiology of hypertension derives from two cases of hemangioendothelioma with plasma levels of ET 10–15-fold greater than in normal subjects. Surgical removal of the tumor led to resolution of hypertension in both cases. In one patient, the tumor recurred along with a rise in plasma ET level and hypertension [15]. Increased plasma ET-1 levels have been shown in patients with essential hypertension by some, but not all investigators.

The role of ET in dialysis-related hypertension has been the focus of active research and controversies. Hypertensive patients with CRF have higher plasma ET-1 levels than normotensive subjects. Elevated plasma ET-1 and ET-3 levels have also been shown in hemodialysis patients, and they have been attributed to either the uremic state or exposure of the cells to an extracorporeal circuit during hemodialysis. Higher ET-1 concentration and mean blood pressure have been observed more frequently in hemodialysis patients than in continous ambulatory peritoneal dialysis (PD) patients.

The Role of Erythropoietin

The availability of recombinant human erythropoietin (rHu-EPO) has improved the management of anemia and the quality of life in patients with chronic renal failure. However, treatment with rHu-EPO frequently results in increased blood pressure, greater requirement for antihypertensive drugs, and potentially increased cardiovascular morbidity. Multicenter trials with rHu-EPO in dialysis patients have shown an increase in diastolic

pressure of >10 mm Hg and the need for increased antihypertensive medications in 88 of 251 (35%) of previously hypertensive patients; a similar increase in BP was noted in 31 of 71 (44%) normotensive patients [16]. The rise in blood pressure usually occurs within 2 – 16 weeks after the initiation of therapy with rHu-EPO. Patients at greater risk for developing hypertension are those with severe anemia, those whose anemia is corrected too rapidly, those with preexisting hypertension, and perhaps those with their native kidneys. The rise in blood pressure has not been observed in patients with normal renal function, suggesting that renal disease may confer a particular susceptibility to the hypertensive action of rHu-EPO.

The level of the hematocrit is important in the regulation of both systemic and renal hemodynamics. Anemia causes a hyperdynamic state characterized by an increase in cardiac output and a decrease in total peripheral vascular resistance (PVR). These charges are necessary to maintain an adequate oxygen supply to peripheral tissues. Left ventricular mass and end diastolic diameter increase in response to this hyperdynamic state. Correction of the anemia with rHu-EPO leads to a decrease in cardiac output and a rise in PVR. Patients who become hypertensive or experience an exacerbation of their blood pressure during rHu-EPO therapy either have an exaggerated rise of PVR in response to the increase in hematocrit, or do not decrease their cardiac output because of reduced compliance, or impaired baroreflex function. The increase in blood viscosity during rHu-EPO therapy correlates with the increase in PVR, but not blood pressure changes. Thus, the rise in blood pressure caused by rHu-EPO cannot be exclusively attributed to changes in blood viscosity. Studies in rats have shown that renal insufficiency is a prerequisite for the development of hypertension during rHu-EPO therapy. This suggests the contribution of other factors, such as enhanced pressor responsiveness to norepinephrine and to Ang II.

In some studies, no vasoconstriction was evident in the isolated rat kidney or isolated human resistance arterioles after infusion of rHu-EPO. In other studies, vasoconstriction was observed in isolated renal and mesenteric resistance vessels of rats. This action was endothelial-independent and not affected by verapamil or phentolamine.

Some studies suggest that rHu-EPO may affect intracellular calcium homeostasis. Others found no correlation between absolute blood pressure levels and platelet intracellular calcium in hemodialyzed patients treated with rHu-EPO.

The administration of rHu-EPO to normal and uremic rats causes a rise in blood and platelet serotonin and an increase in blood pressure. These effects were abolished by ketanserin, an antagonist of 5-hydroxytryptophan (5-HT_2) receptors. The study suggests that serotonin may play a role in the development of hypertension caused by rHu-EPO.

Others have shown that hemodialysis patients on rHu-EPO therapy manifest increased ET-1 levels.

There is no evidence that decreased NO is responsible for rHu-EPO-associated hypertension, because rHu-EPO stimulates NO production.

The Role of Divalent Ions and Parathyroid Hormone (PTH)

A relationship between platelet or lymphocyte intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) concentration and blood pressure has been demonstrated in patients with essential hypertension, as well as in patients with ESRD. The mechanisms leading to the increase in $[Ca^{2+}]i$

are not clear. This could be the result of increased circulating pressor hormones, such as NE or Ang II, or increased secretion of an ouabain-like factor in response to volume expansion. Finally, the increase in $[Ca^{2+}]i$ in vascular smooth muscle cells could be caused by secondary hyperparathyroidism. CRF is frequently associated with secondary hyperparathyroidism, which leads to increased $[Ca^{2+}]i$.

Recently, Raine et al. [17] studied 36 patients with chronic renal failure, 10 with normal serum PTH levels, 17 with elevated serum PTH, and 9 with elevated PTH but treated with nifedipine. Platelet $[Ca^{2+}]i$ was significantly greater in the 17 patients with increased serum PTH than in patients with normal serum PTH. In addition, a significant relationship was present between serum PTH and platelet $[Ca^{2+}]i$ or between platelet $[Ca^{2+}]i$ and mean blood pressure and between PTH and mean blood pressure. In patients with high serum PTH receiving nifedipine, platelet $[Ca^{2+}]i$ was not increased. Nine patients with hyperparathyroidism were restudied during treatment with alfacalcidol, a vitamin D metabolite. In these patients, serum PTH, platelet $[Ca^{2+}]i$ and mean blood pressure all decreased significantly. The changes in blood pressure during treatment with alfacalcidol were linearly related with the changes in serum PTH and in $[CA^{2+}]i$. These studies suggest that increased serum levels of PTH may be responsible for both the rise in $[Ca^{2+}]i$ and the increase in blood pressure in these patients. Treatment of secondary hyperparathyroidism with oral calcium may reduce blood pressure in hemodialysis patients.

Dialysis patients may occasionally develop hypercalcemia as a result of exogenous administration of vitamin D analogs, oral calcium supplementation, granulomatous diseases, multiple myeloma, or severe secondary hyperparathyroidism. In these patients, hypercalcemia may either aggravate or cause hypertension. Hypercalcemia is more likely to raise blood pressure in the presence of increased serum levels of PTH, and it does so primarily by increasing systemic vascular resistance, whereas cardiac output usually remains unchanged.

In rats with CRF, acute hypercalcemia raised blood pressure more than in normal rats [18]. This appeared to be secondary to the state of secondary hyperparathyroidism, because parathyroidectomy reduced the pressor response to acute hypercalcemia. These studies suggest that the presence of the parathyroid hormone plays an important role for the hypertensive action of hypercalcemia in uremic rats.

The Role of Cyclosporin A

Cyclosporin A is a potent orally active immunosuppressive agent used in the management of patients with a variety of renal diseases and with organ transplantation. It is known to be nephrotoxic and to raise blood pressure. The mechanisms of cyclosporin-induced hypertension are complex. It increases possibly because of direct action on vascular smooth muscle cells or activation of the sympathetic nervous system. Cyclosporin increases the activity of efferent sympathetic nerves and decreases the fractional excretion of sodium. Renal denervation and alpha-blocking agents prevent the decrease in renal blood flow (RBF) caused by cyclosporin.

The role of the sympathetic nervous system in cyclosporin-induced hypertension is less clear. Plasma and urinary catecholamines do not change during administration of this drug, but these levels are a poor marker of regional sympathetic nervous system activity. The role of the renin-angiotensin system is also uncer-

tain. Acute administration of cyclosporin increases PRA, but chronic treatment does not.

Cyclosporin increases the production of thromboxane A_2 and inhibits the production of prostaglandin E_2. Administration of inhibitors of thromboxane lessens cyclosporin's renal hemodynamic effects. Cyclosporin also increases the concentration of serotonin in the blood and platelets. It can cause magnesium deficiency, which may also cause increased PVR.

Pathophysiology of Hypertension in Specific Renal Parenchymal Diseases

Glomerulonephritis

In acute glomerulonephritis with endocapillary proliferation, e.g. poststreptococcal glomerulonephritis, the urine output and sodium excretion are reduced leading to volume expansion, increased cardiac output and hypertension. PRA is usually normal or reduced. Interestingly, in acute forms of glomerulonephritis characterized by extracapillary proliferation (e.g. Goodpasture, crescentic glomerulonephritis, and microscopic vasculitis), hypertension is mild or absent, despite the frequent coexistence of oliguria or anuria. Thus, sodium retention and volume expansion are not the only factors responsible for the rise in blood pressure in these conditions.

In chronic forms of glomerulonephritis, hypertension is very common, and the prevalence is highly conditioned by the type of histologic lesion and the presence or absence of renal insufficiency.

In minimal change disease, the prevalence of hypertension is very low. It increases with the age of the patient and probably is not greater than in the general population matched for age and ethnic background.

In patients with membranous glomerulonephritis, the prevalence of hypertension is approximately 10%, but this value rises with worsening renal function.

In patients with focal and segmental glomerulosclerosis, the prevalence of hypertension is very high at the time of discovery of the disease (42% at onset), due in part to the impaired renal function. Blood pressure increases as renal function deteriorates .

Hypertension is also common among patients with *IgA nephropathy*. In a retrospective analysis of 374 patients, 36% of subjects had hypertension at the time of renal biopsy, while only 24% had renal insufficiency. After an average follow-up of 5 years, 63% of patients were hypertensive and 46% had impaired renal function [19]. This prevalence of hypertension in IgA glomerulonephritis is higher than in the healthy population, and has been confirmed [20].

D'Amico et al. have shown that the prevalence of hypertension in patients with IgA nephropathy varies with the type of renal histological lesion. Glomerular sclerosis, interstitial fibrosis and arteriolar hyalinosis were more likely to be associated with hypertension [21]. The presence of hypertension in patients with IgA nephropathy is associated with an adverse renal outcome. The 3 year renal survival is 70% after the onset of hypertension, and treatment of hypertension, particularly with an ACE inhibitor, may prolong the renal survival.

The pathophysiology of hypertension in IgA glomerulonephritis is uncertain. Zucchelli et al. [20] found normal levels of exchangeable sodium, whereas Valvo et al. [22] found expanded blood volume in both nor-

motensive and hypertensive patients with IgA nephropathy. Valvo et al. described increased PVR in hypertensive patients and suggested that this might be related to increased sympathetic nervous system activity, but Zucchelli et al. found normal plasma NE levels in these patients.

Among patients with membrano proliferative glomerulonephritis (MPGN), hypertension is present in about 30% of patients at the onset of the disease, and the prevalence increases with worsening renal function.

Diabetes Mellitus (DM)

Diabetes mellitus and hypertension are commonly associated, and their frequency is increasing as our patient population ages. Diabetic patients show a higher prevalence of hypertension, particularly when diabetic nephropathy ensues. Hypertension in diabetic patients greatly increases the risk of cardiovascular disease, nephropathy, and retinopathy. Treatment of hypertension appears to delay the onset of these complications.

The pathophysiology of hypertension in diabetic patients is poorly understood. However, genetic factors, insulin resistance, abnormalities of sodium and calcium metabolism, increased activity of the sympathetic nervous system, and endothelial dysfunction appear to play a role.

In patients with insulin Type I DM, hypertension often develops in connection with the appearance of nephropathy. Patients without nephropathy usually remain normotensive. This has led some investigators to suggest that the susceptibility to renal disease in Type I DM patients is associated with a genetic predisposition to hypertension.

In patients with Type II DM, hypertension may follow but often precedes the development of diabetes. Several studies have shown increased serum insulin concentrations in a substantial number of patients with essential hypertension and in normotensive offspring of hypertensive parents. Elevated insulin levels in patients with essential hypertension are a compensatory response to a defect in insulin-stimulated glucose uptake. This has led many investigators to postulate a causal relationship between hyperinsulinemia and hypertension, although this notion is not universally shared. Hyperinsulinemia is not present in some ethnic groups with high prevalence of essential hypertension, and hypertension is rare in ethnic groups, such as the Pima Indians, with a high prevalence of insulin resistance and hyperinsulinemia. Moreover, in some studies the relationship between hyperinsulinemia and hypertension could entirely be accounted for by obesity and age. In other studies, the relationship was found in individuals with normal body mass index, and in one study a negative correlation between hypertension and hyperinsulinemia was found.

Repetitive hyperinsulinemia occurring during food ingestion rather than baseline secretion could provide the stimulus for hypertensive mechanisms, such as sodium retention [23], stimulation of the sympathetic nervous system [24], and alteration of cation transport.

The causal relationship between hyperinsulinemia and hypertension remains controversial, mostly because administration of insulin leads to vasodilatation rather than vasoconstriction. It appears more likely that insulin resistance, rather than hyperinsulinemia, may be linked to hypertension. Resistance to the vasodilator action of insulin could lead to a rise in PVR and hypertension.

Some evidence suggests that alterations of calcium metabolism may contribute to insulin resistance and may cause increased PVR, exaggerated pressor response to vasoactive substances and hypertension in Type II DM patients.

Autosomal Dominant Polycystic Kidney Diseases (ADPKD)

Hypertension is very common in patients with ADPKD. In the series of Zeier et al. [25] the prevalence of hypertension, defined as casual blood pressure ≥ 140/90 mm Hg, was as high as 82% in adults with ADPKD and normal renal function, and in virtually all ADPKD patients with impaired renal function. The rise in blood pressure may occur at a young age, even before any demonstrable manifestation of renal involvement. In a study of children and adolescents with ADPKD, circadian blood pressure profile, particularly nocturnal blood pressure, was significantly higher in patients with the disease than in matched controls, although most values were still <140/90 mm Hg. Left ventricular mass index was also significantly higher in children and adolescents with ADPKD than in matched controls.

The pathophysiology of hypertension in ADPKD is probably multifactorial [26]. Some studies have shown that patients with ADPKD, even with a normal GFR, have a reduced ability to excrete an acute sodium load and have an expanded extracellular volume and reduced PRA levels [27]. Certainly, hypertension in patients with ADPKD is sodium -sensitive, and dietary sodium restriction consistently decreases blood pressure in these patients. This is also substantiated by the presence of higher levels of atrial natriuretic peptide (ANP) in hypertensive patients with ADPKD than in controls [25].

Hypertensive ADPKD patients with normal or near normal renal function have a significantly higher intracellular sodium concentration and fractional sodium excretion, and a lower rate for ouabain-sensitive sodium efflux from erythrocytes. Studies suggest that abnormal cell sodium handling may play a role in the pathophysiology of hypertension in these patients.

Other studies have shown higher PRA levels in patients with ADPKD than in age- and blood pressure-matched controls. By immunostaining for renin, Graham et al. found hyperplasia of the juxtaglomerular apparatus in ADPKD kidneys [28]. The activation of the renin-angiotensin system seems to be a function of cyst size and rate of growth [29]. Renin concentration was increased in ADPKD cyst fluid compared with the concentration in fluid from simple renal cysts, and renin mRNA was expressed in the tubulocystic epithelium of patients with ADPKD, suggesting that the tubulocystic epithelium has the potential to synthesize renin. ACE inhibitors reduce blood pressure and renal vascular resistance without altering glomerular filtration rate (GFR) or urinary excretion of kallikrein and PGI2 in these patients. These studies suggest that the decrease in renal blood flow in patients with ADPKD is due to activation of the renin-angiotensin system and that ACE inhibitors may be of particular value in the treatment of these patients. Harrap et al. [30] showed that reduced renal blood flow, higher PRA, and increased body sodium levels precede hypertension, because these changes occur in normotensive individuals with ADPKD.

There is also increased release of ET into the stretched and narrow arterioles and increased afferent nerve activity from the kidneys that may lead to an increase in sympathetic nervous system activity. Iversen et al. [31] found that muscle sympathetic nervous system activity was higher in patients with hypertension and ADPKD than in normal controls. However, in a different study, plasma NE levels were not different between hypertensive and normotensive patients with ADPKD [32].

Hydronephrosis

Hypertension is very common among patients with hydronephrosis. The exact mechanisms of hypertension in these patients are unknown, but an imbalance between vasoconstrictors, such as Ang II, and vasodilators, such as kallikrein, may play a role. In dogs with unilateral midureter occlusion, Vaughan et al. [33] observed a transient rise in blood pressure and in the activity of the renin-angiotensin system. After 6 months of ureteral occlusion, PRA was normal, but NE levels were elevated in the kidney with ureteral occlusion.

Among eight patients with unilateral hydronephrosis and hypertension, peripheral PRA was normal in 7 and borderline high in 1 [34]. Four patients had hydronephrotic/contralateral kidney renin ratio > 1.5, suggesting excessive renin release from the diseased kidney. Nephrectomy normalized blood pressure in each of these patients. This study suggests that hypertension associated with unilateral hydronephrosis is partly renin dependent.

In patients with bilateral ureteral obstruction and decreased GFR, sodium retention and volume expansion also occur and participate in the genesis of hypertension. In these patients, relief of the obstruction result in postobstructive diuresis with a rapid normalization of the excessive volume and blood pressure.

The role of renal afferent nerves in the pathogenesis of hypertension associated with hydronephrosis has not been explored.

Chronic Pyelonephritis

There is an increased prevalence of hypertension in patients with pyelonephritis: 10% in children, 33% in adults, and 46% after a mean follow-up of 69 months [35]. The pathogenesis of hypertension in this condition is uncertain. However, the presence of increased PRA in renal venous plasma from the diseased kidney in unilateral pyelonephritis lends support to the role of renin in the hypertension of chronic pyelonephritis.

Acute Renal Failure

The prevalence of hypertension is extremely high in patients with ARF due to glomerular or vascular diseases (approaching 90% in the more severe forms), but it is lower (10 – 15%) in patients with tubular-interstitial diseases. The pathophysiology of hypertension in ARF has not been well defined. Improvement of renal function in these patients results in resolution of hypertension in the majority of cases.

Hypertension is a frequent but not universal finding in patients with renal atheroembolic disease. When it occurs, it is often episodic, difficult to control, and probably related to activation of the renin-angiotensin system. The sporadic hypertension in this disorder may be related to repeated showers of atheromatous material to the kidney resulting in renal ischemia, activation of the renin-angiotensin system, and hypertension.

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Renovascular Hypertension

Michael B. Ganz and Allen Averbook

Renovascular hypertension is one of the more common causes of secondary hypertension with reports of its frequency varying from < 1% in unselected patient populations to as much as 20% in patients referred to special centers [1 – 3]. By definition, renovascular hypertension refers to hypertension caused by renal hypoperfusion – a decrease in blood flow to the kidney [4]. Therefore, the presence of a solitary stenotic renal artery lesion does not establish the diagnosis of renovascular hypertension. It is absolutely necessary for renal ischemia to occur, and this happens when stenosis is > 75% of the luminal diameter [4 – 6]. This, in turn, sets off a cascade of events that leads to the stimulus that raises blood pressure; hence the diagnosis of renovascular hypertension. Most importantly, renovascular hypertension is an important diagnosis to make in that it the most common curable form of hypertension and is one of the few potentially reversible causes of chronic renal failure (CRF)[1]. This chapter describes pathophysiologic mechanisms in renovascular hypertension, clinical features of the disease, and staging of suspicion for disease to select appropriate diagnostic steps. New therapeutic options are reviewed, and the advantages and disadvantages of each are delineated.

Pathophysiology of Renovascular Hypertension

Renovascular hypertension in humans is the result of a stenotic lesion leading to ischemia that, in turn, initiates events that lead to hypertension (Figure 1) [4, 7]. The pathophysiologic state of ischemia serves as the stimulus for a release of renin. Resultant high levels of angiotensin II (Ang II) levels then readily increase renal vascular resistance causing a shift in the pressure-natriuresis curve [6, 8]. In this second phase of renovascular hypertension, volume is increased and quite often maintained despite markedly elevated blood pressure further accentuating the hypertension [6, 9]. The patient then exhibits the symptoms of sudden and significant hypertension, such as pounding headaches and palpitations.

Renal ischemia can continue for several years undetected. After years of renal ischemia, many patients may then enter a third phase of the disease. In these patients, regardless of whether the stenotic lesion is relieved or not, hypertension continues unabated. It is at this stage that widespread arteriosclerosis with concomitant glomerulosclerosis has already occurred in the contralateral, or non-stenotic, kidney [1, 9]. These pathophysiologic changes, specifically glomerulosclerosis along with medial hyperplasia of the blood vessels, are the result of the prolonged exposure to high blood pressures (and conse-

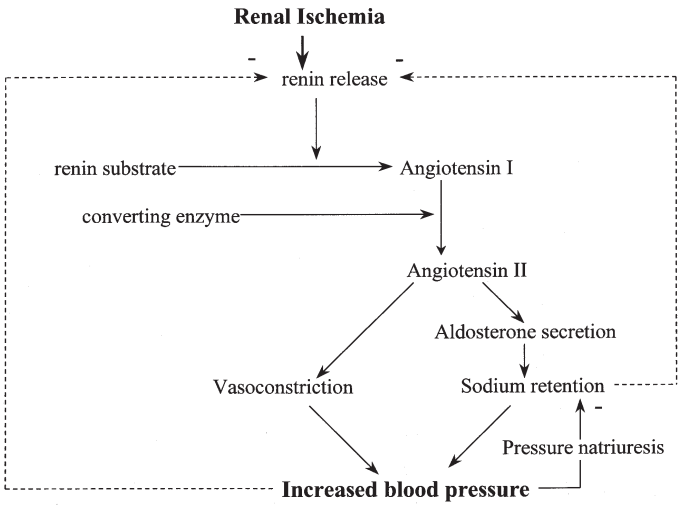

Figure 1.

quently increased glomerular pressures) in addition to the high levels of Ang II [1, 9]. The clinical relevance of this is that the sooner the lesion responsible for the renal ischemia is relieved, the greater chance of alleviating the hypertension and thereby preserving renal parenchymal tissue [1, 4].

The pathophysiology of the patient with bilateral disease is a little different than that seen with a solitary lesion. In patients with bilateral disease, cardiac output is usually greater than in those with unilateral disease [4, 7, 10]. Therefore, the hypertension in the patient with bilateral renal artery disease is more dependent on volume. The most likely etiology for this difference is that stenosis does not develop symmetrically in the 2 kidneys. Presumably, most bilateral stenotic lesions are initially an undetected unilateral lesion. Thus, parenchymal disease will develop in the contralateral kidney during the years of prolonged hypertension before the development of a stenotic lesion on the unaffected side. The hypertensive kidney disease would then impair the pressure natriuresis by which the contralateral kidney (nonstenotic side) normally maintains the classic high-renin-normal volume pattern of unilateral renal artery stenosis. This volume retention would be further exacerbated when the second stenotic lesion develops in the contralateral kidney. During this phase of the renovascular disease, the stenotic kidneys then chronically continue to secrete excess renin with the resultant elevation in peripheral resistance and fluid volume [7].

Other factors have been proposed that may be interrelated with the primary renin-angiotensin mechanism of hypertension of renovascular hypertension. Recent studies have implicated increased sympathetic nervous system activity and enhanced vasopressin response as potentially important physiologic responses contributing to the hypertension of renovascular disease. Moreover, reduced vasodilatory prostaglandins have been seen in patients with renovascular hypertension [1, 6]. These prostaglandins are necessary to maintain renal blood flow (RBF). This finding may have important clinical applicability in that the use of nonsteroidal anti-inflammatory agents (NSAID; such as ibuprofen) may acutely decrease blood flow by further inhibiting prostaglandin production. This decrease in blood flow may lead to a further decrease

Table 1.

Characteristics	Essential Hypertension (%)	Renovascular Hypertension (%) Atheroma	Fibromuscular Dysplasia
Race (African-American)	29	7	10
Family history	67	58	41
Age at onset: < 20 years	12	2	16
> 50 years	7	39	13
Obesity	38	17	11
Abdominal bruit	7	41	57
Elevated renin profile	15	80	80
Smoking	42	88	17
Hypokalemia (K < 3.4 mEq/L)	7	14	71

in renal function and a subsequent increase in blood pressure.

Clinical Features

Variable clinical features of renovascular hypertension dominate in one of 2 patient groups (Table 1). The prevalence of renovascular hypertension is unknown in that results from all major studies, save one, were based predominantly on clinical assessments. The investigators did not use angiography to look for stenosis. Therefore, the prevalence rates are an underestimation of renal artery stenosis. However, renovascular hypertension prevalence is probably anywhere from 0.1 – 5% in the general hypertensive population and may be as high as 20% in those individuals with severe hypertension [1, 11 – 14]. Moreover, in Whites with more severe hypertension, there is a 6-fold greater prevalence than in the African-American population with similar blood pressure levels.

Lesions of Renovascular Hypertension

The 2 major causes of renovascular hypertension are atherosclerosis and fibromuscular dysplasia (FMD) [12, 15 – 18]. In those individuals with atherosclerosis, quite often the finding of a middle-aged, white male with other evidence of atherosclerotic disease (claudication, angina) raises the possibility of progressive renal artery atheromatous plaque formation leading to stenosis. In addition, these individuals may have a recurrent history of unexplained pulmonary edema and/or renal dysfunction prior to the hypertension becoming more prominent. A significant history of smoking increases the possibility that the hypertension seen is related to atheromatous renal artery disease; 88% of those with atheroma renal artery hypertension were smokers, while approximately 42% of those with essential hypertension had a similar history [18]. One laboratory test that may aid in suggesting renovascular hypertension in con-

junction with clinical clues is significant hypokalemia with nephrotic-range proteinuria (> 3.5 g/24hours).

The anatomic location of the atherosclerotic plaque has significant therapeutic implications. The atheromatous plaques occur most commonly in the proximal one-third of the renal artery [2, 13, 19]. Other less common areas for plaque formation are the distal region of the renal artery and the ostium of this same blood vessel. Ostium lesions form directly from aortic atheromatous lesions [18]. More importantly, these ostial lesions are less responsive to angioplasty therapy than proximal lesions (see *Therapy*) and quite often progress in a more aggressive fashion. Renal artery stenosis secondary to atherosclerotic disease has been studied both retrospectively with angiography and prospectively with renal duplex ultrasound. Rates of anatomic progression varied from 36 – 71% of patients. Progression to occlusion occurred in 8 – 16% of patients over a 3- to 5-year period [18, 20]. The rate of progression to total occlusion occurred more frequently when there was a higher grade stenosis on the initial angiogram. In the prospective study by Zierler et al. [21] renal arteries that were normal on first exam did not have any progression of disease, but the cumulative incidence of progression from < 60% renal artery stenosis to ≥ 60% was 23% ± 9% at 1 year and 42 ± 14% at 2 years. Those renal arteries that progressed to occlusion all had ≥ 60% stenosis at the initial visit with the cumulative incidence of progression to occlusion being 5% ± 3% at 1 year and 11% ± 6% at 2 years. The overall progression of renal artery stenosis in this study was about 20% per year.

In younger patients, especially in white females, FMD is the most likely etiology for renal artery stenosis [15, 17]. Rare in the black population, FMD should be considered when a young white female (< 20 years of age), without any family history of hypertension, develops moderate to severe hypertension. The lesion in FMD is classified into 4 types. The most common variant is that of medial fibroplasia, which constitutes 75% of all cases. It progresses less frequently than atheromatous lesions and produces the classic beaded appearance on angiograms. This appearance is the result of areas of medial thickening interspersed with aneurysmal dilations. Intimal, perimedial, and periarterial lesions are the more sharply localized fibrodysplastic lesions and progress to greater stenosis more rapidly [17]. Without intervention significant stenosis with concomitant hypertension can develop, and subsequent significant renal disease will ensue. FMD will progress in one-third of patients and may develop in contralateral vessels, but it rarely results in renal artery occlusion [3].

Diagnosis

Clinical Clues

Renovascular hypertension must be excluded as the etiology for hypertension in patients with hypertension. While extensive screening of all hypertensive patients is clearly impractical, certain clinical clues will help establish an index of suspicion and thereby justify further evaluation (Table 2). The indices of suspicion for renovascular hypertension are low, moderate, and high. The clinical index of suspicion serves as a sensible diagnostic guide for the patient with hypertension and suspected renovascular disease. Patients can then be examined and their history reviewed for potential signs and symptoms that may suggest underlying renovascular disease.

Table 2. Clinical Index of Suspicion: Guide for Selecting Patient Work-ups

Low (most should not be tested)
- borderline mild or moderate hypertension without any clinical evidence of vascular disease

Moderate (noninvasive tests recommended)
- diastolic blood pressure > 120 mm Hg
- hypertension refractory to standard therapy
- abrupt onset of hypertension; < 20 or > 50 years of age
- hypertension with an abdominal bruit
- diastolic blood pressures > 105 in a patient who smokes, has evidence of peripheral vascular disease, and/or unexplained azotemia
- rapid normalization of blood pressure with an ACE inhibitor in a patient with moderate hypertension who smokes and has evidence of peripheral vascular disease.

High (may consider proceeding directly to angiography)
- diastolic blood pressure > 120 mm Hg in a patient with either progressive renal disease and/or a patient with vascular disease that has not responded to aggressive antihypertensive treatment.
- accelerated or malignant hypertension
- hypertension with recent elevation of serum creatinine
- moderate or severe hypertension with incident detection of renal asymmetry

Most importantly, the patient with diabetes mellitus (DM), especially noninsulin-dependent diabetes (NIDDM, type II), should warrant a closer evaluation for possible renovascular disease. Many diabetic patients, while they will develop nodular glomerulosclerosis as a result of diabetic nephropathy, leading to hypertension, also have progressive and diffuse atherosclerotic vascular disease [14, 19, 22]. This is yet another manifestation of their DM, as their lipid profiles are quite often abnormal even in the face of normal renal function. The etiology for difficult blood pressure control and/or a more rapid decline than expected in renal function in these patients may suggest the presence of undetected renal artery stenosis. Therefore, the index of suspicion should be high in a diabetic patient with other manifestations of atherosclerotic disease.

The patient with well-controlled hypertension would fall into the low category. The prevalence of renovascular disease is likely to be <1%, with most of the positive test results turning out to be falsely positive. However, the patient who presents with a more complicated clinical picture, such as difficult-to-control blood pressure (diastolic blood pressures > 120 mm Hg) that appears to be refractory to standard therapy and/or abrupt onset of hypertension before the age of 20 or after the age of 50, should undergo aggressive evaluation.

An abdominal bruit is one clinical feature with clear discriminatory value in patients with renovascular hypertension. Heard in almost half of all patients with renovascular hypertension, an abdominal bruit is heard over the flank in only 9% of patients with essential hypertension. A bruit that is high-pitched with systolic and diastolic components and that radiates laterally strongly suggests functionally significant renal arterial stenosis. However, the absence of an abdominal bruit does not exclude renovascular hypertension.

Diagnostic Tests

The evaluation of hypertensive patients to identify a causative renal artery lesion depends on whether there is a low, moderate, or high level of suspicion for underlying renovascular hypertension [23]. Unfortunately, there are no perfect screening tests for its

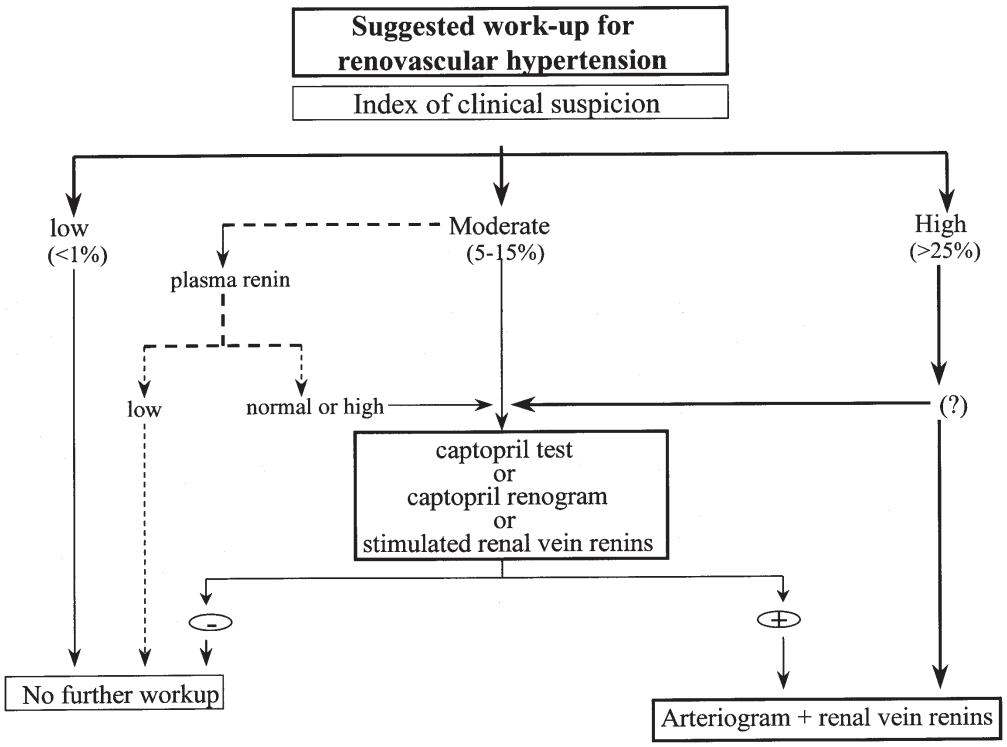

Figure 2.

detection. The major tests can be classified into 2 categories (Figure 2): physiologic and anatomic. Physiologic tests can be readily performed on an outpatient basis and do not indicate the involved kidney. These inexpensive tests are the measurement of peripheral plasma renal activity (PRA) and the captopril test and should be performed in those patients with a moderate level of suspicion for renovascular hypertension [23].

The second category includes tests that provide anatomic functional information about each kidney. These tests should ideally follow the noninvasive office visit tests. However, a noninvasive work-up should include a renal ultrasound to look for asymmetry in the patient with suspected disease followed by PRA and/or a captopril test.

PRA/captopril test. Approximately 75% of all patients with proven renovascular hypertension have markedly elevated PRA [24]. While this test can be normal in value, it is rarely, if ever, low in a patient with renovascular hypertension. Unfortunately, its predictive value in the absence of clinical clues for renovascular hypertension is low. It has a sensitivity of 57% and should not be used as a screening test for all hypertensives. In view of the limitations of the PRA test, alternative maneuvers have been used to enhance the sensitivity of the test. Of these, the response of PRA to captopril has been widely used.

The captopril test has been found to be the most reliable for distinguishing patients with renovascular hypertension [24]. For the test, the patient should maintain a normal salt in-

take, and, if possible, all antihypertensives (including diuretics) should be withdrawn 3 weeks before the test. This test involves measuring plasma renins in the seated patient after the administration of the angiotensin-converting enzyme (ACE) inhibitor captopril. The plasma renin response is classically greater in patients with renovascular hypertension than in those with essential hypertension. The criteria for distinguishing patients with renovascular hypertension are an absolute increase of 10 ng/mL/hour, a post-captopril level of > 12 ng/mL/hour, and/or a percentage increase of ≥ 150% in renins and/or ≥ 400% if the baseline PRA is < 3 ng/mL/hour. The sensitivity and specificity of this test is approximately 75% and 90%, respectively. However, this test is less reliable in patients with preexisting renal disease, thereby making it difficult to interpret in patients with renal insufficiency. In addition, it cannot distinguish between unilateral and bilateral disease, although it is positive in both of these diseases.

More involved tests to ascertain the presence of renal artery stenosis include renal vein renin determinations, renal scintigraphy, captopril renography and intravenous digital subtraction. Renal vein determinations measure renins through catheter placement in the patient's inferior vena cava. An increase of 25% is found in patients with renovascular hypertension and is usually 50% more in the ischemic kidney. No (or little) increase is found in the contralateral kidney. Renal scintigraphy, on the other hand, involves the use of iodohippurate sodium I^{131} that is selectively taken up by the kidney. However, this test has an unacceptably high rate of both false-positive and false-negative results and is relatively expensive.

The advantage of captopril renography is that it is based on the principle that glomerular filtration rate (GFR) and RBF of an ischemic kidney depend on the effects of angiotensin on the efferent glomerular arterioles and fall markedly with the administration of an ACE inhibitor [14]. The sensitivity and specificity of this test are relatively high (90 – 95%), but there is a low sensitivity (50 – 75%) in distinguishing between renovascular and renal parenchymal disease. Intravenous digital subtraction angiography was introduced with great fanfare. It involves visualization of the renal arteries without the potential complications of arteriography. However, this test suffers from the need for a large dye load, and it has poor resolution in obese patients. Most importantly, the most common atherosclerotic lesion, proximal stenosis, is often missed. Lastly, a promising and relatively noninvasive method of CO_2 injection has begun to be tested in patients with suspected renovascular hypertension. This method involves CO_2 injection and digital subtraction angiography to visualize the aorta and renal arteries. This procedure is currently in the phase of clinical validation and holds great promise for routine clinical use in patients with renovascular disease.

In facilities with an experienced technician in the use of duplex scanning, this should be the initial screening test [14, 16, 21]. However, in the patient with high suspicion and who is a candidate for angioplasty, the clinician should proceed directly to arterial angiography. This procedure provides an immediate answer as to whether there is renovascular disease and whether it is potentially curable [14, 19, 23]. Unlike the other studies, arteriography allows one to see the renal vascular architecture for potentially invasive therapy (i.e. surgical revision). Patients with a high index of suspicion should more than likely have a renal arteriogram, without the need for captopril studies. The predictive value of an arteriogram in patients with a high likelihood for disease is 32%, thereby justifying proceeding with this test first. Although

renal arteriography is almost always successful in diagnosing renovascular hypertension, it has relatively little value in determining surgical curability of renovascular hypertension.

Treatment

Once a physiologically and hemodynamically significant renal artery stenosis has been identified, the physician is still left with the question of how best to treat the lesion. Depending upon how one interprets the data, the literature can be used to support any of the 3 main treatment options: percutaneous transluminal angioplasty (PTA) with or without stent placement, operative intervention, or drug therapy. The character and known natural history of the lesion along with the patient's medical condition all influence the decision regarding treatment choice.

Quite often with the progression of renal artery stenosis there is an increase in serum creatinine, reflecting progressive renal dysfunction [4, 21]. Good blood pressure control through medical therapy does not seem to delay the progression of renal artery stenosis [18]. In comparing the value of drug therapy and operation, one study looked at an equal number of similar patients over a 7- to 14-year period [1]. In this study, 84% in the operation group survived and 93% were cured or showed significant improvement, whereas only 66% of those in the drug therapy group survived through the length of the follow-up period. Of those, 21% ultimately required operation for uncontrollable hypertension. Moreover, mortality in the medically treated group was significantly higher than that of the operation group. These differences applied to patients with both atherosclerotic and fibromuscular lesions of the renal artery.

Barring prohibitive medical risks, therefore, intervention for symptomatic renal artery stenosis is unquestionably justified, not only for blood pressure maintenance, but also for possible prevention of deterioration in renal function. An aggressive approach to renal revascularization is appropriate given the excellent outcomes of current surgical techniques with perioperative morbidity and mortality rates of 0 – 8% [12, 25]. Candidates for intervention include all patients with severe, difficult-to-control hypertension regardless of the nature or location of renal artery lesions (i.e. main stem vs. arterial branches, bilateral renal artery involvement), extrarenal vascular disease, or associated cardiovascular disease that may actually benefit from control of systemic hypertension. Age, duration of hypertension, type of lesion (fibromuscular vs.atherosclerotic), or the distribution and location of arterial lesions are not good determinants of successful outcomes following intervention. Clinically evident coronary artery disease, age > 70 and a serum creatinine > 3mg/dL, are co-morbid risk factors that may influence outcomes but should not necessarily preclude aggressive intervention on their own merits. The choice of PTA vs.surgical revascularization needs to be individualized.

Main renal artery FMD should be treated with PTA. When PTA is carried out by an experienced interventionalist, technical and clinical success rates with 2-year patency rates > 90% are usually reported. The results for nonorificial atherosclerotic lesions are similar, but these comprise only 15 – 20% of all atherosclerotic renal artery lesions, while the majority are orificial in that they are extensions of disease from the aorta. When reading the literature, one must look critically at the assumptions being made to define outcomes, differentiate between technical and clinical success, and note the length of follow-

up, especially with consideration of the natural history of the disease process in mind.

In the only prospective, randomized comparison of renal artery PTA with surgery, Weibull et al. [26] found a 2-year primary patency rate of 75% for renal PTA and 96% for operation. The secondary patency rate in the PTA group was 90% and in the surgical group 97%, yet nearly half of those patients with initial PTA failures underwent secondary surgical revascularization to achieve the quoted 90% secondary patency rate. On the basis of this study, we would find it difficult to recommend renal PTA as the initial treatment of choice in all-comers. Other studies have reported an 80% technical success rate with 68 – 90% clinical success and 5-year patencies as high as 88% following PTA in some series [1, 27]. In the literature, PTA results in 44 – 65% long-term improvement in blood pressure as compared to surgery, which is reported to yield sustained improvements of 90 – 93%. Renal function has been maintained or improved in 40 – 88% of patients following PTA and 70 – 94% of patients following surgical revascularization. In summary, PTA of ostial atherosclerotic lesions or fibrodysplastic lesions involving the renal artery branches yields outcomes inferior to that seen with surgical revascularization [28].

Whether or not these results can be improved upon by combining renal artery stent placement with PTA remains uncertain. The use of renal artery stents in combination with PTA as compared to surgical revascularization has not yet been studied in a prospective, randomized fashion. The published data thus far suggest that stenting of renal ostial stenoses has a higher initial success rate and improved intermediate term patency rate over PTA alone [29 – 31]. However, the benefits of PTA with stenting as compared to surgery are still unclear. Clinically, stents are indicated when significant elastic recoil exists in an artery undergoing PTA, dissection occurs following PTA, or restenosis develops following PTA. Placement of a stent in the renal artery will preclude certain surgical methods of revascularization. Proximally-placed stents will prevent the surgeon from performing aortorenal endarterectomy, should an operation become a consideration. Stents in the main portion of the body and especially those that encroach on the distal branch points will affect any subsequent surgical reconstruction that can be employed and potentially increase the difficulty of surgery. These factors must be taken into account if PTA with stenting is going to be offered as a therapeutic modality. Some of the complications related to PTA and/or stenting of the renal artery include arterial spasm, acute arterial occlusion, arterial perforation, embolization, and dye-related renal failure. Needless to say, good hydration prior to, during, and after the study is an important part of the management of these patients. With regard to blood pressure improvement or reversal and renal function, the results with the use of stents do not appear to be any different than those seen with successful PTA. The use of PTA with or without stents may be appropriate for initial therapy in those with amenable lesions as described above, but the primary patency and clinical benefits of these procedures in all other patients do not yet appear comparable to those seen with surgical revascularization.

Once surgical revascularization has been decided upon, certain preoperative measures must be followed to optimize the surgical outcome. The patient's blood pressure must be adequately controlled to maintain near normal diastolic pressures. By the same token, the antihypertensive medications should be reduced to the minimum required while in hospital to maintain an adequate blood pressure. Importantly, the patient is appropriately hydrated in preparation for surgery and opti-

mized from a cardiopulmonary standpoint – in an intensive care unit (ICU) if necessary.

A variety of surgical techniques are available to the experienced vascular surgeon in order to achieve successful renal revascularization. The standard surgical approaches include aortorenal endarterectomy and aortorenal bypass. In the first approach, the aorta is opened transversely or transaortically depending upon the surgical requirements, and the diseased intima is endarterectomized to include its extension into the renal arterial orifices. This can be done for unilateral or bilateral disease and is becoming a desirable approach when concomitant aortic grafting is to be performed. Aortorenal bypass with either autologous or synthetic conduits can be performed with relative ease if the aorta itself is not too diseased to preclude safe application of a clamp or when aortic replacement with synthetic graft is also being performed. Using the diseased aorta itself as an inflow source when aortic replacement is not indicated has caused some surgeons to prefer the performance of nonanatomic bypasses. Other circumstances that might also suggest the use of alternative revascularization techniques include increased operative risk, anatomic considerations, bilateral disease, a desire to avoid the aorta secondary to scarring or disease, or the preference for a non-midline incision to avoid potential respiratory or gastrointestinal consequences associated with such an incision. The most commonly performed extra-anatomic bypasses are hepatorenal or splenorenal bypasses. Other less commonly used alternatives include iliorenal, superior mesenteric artery (SMA)-renal, and supraceliac aorto-renal bypasses. Each of these techniques has pros and cons too extensive to address here, but the nature of the disease, patient anatomy, and prior surgical history along with current medical condition will dictate the procedure to perform. Aside from iliorenal bypasses and possibly SMA – renal bypasses, which for technical reasons are less desirable approaches in most circumstances, the above-named techniques all should have similar outcomes when performed well.

One other technique, ex vivo reconstruction, is required when there is FMD and aneurysms or stenoses involving renal artery branches, renal artery dissection, congenital abnormalities of the branches requiring resection, and patients with prior grafts or surgery to the distal renal artery. This technique involves mobilization and removal of the kidney from its bed with either autotransplantation to another site (i.e. the iliac fossa) or replacement in its native bed.

Each of these techniques has its advocates. In appropriately selected patients and technically well-performed surgery, the outcomes for each are similar with one caveat. In combined aortic replacement and renal revascularization, there is increased morbidity and mortality as compared to the other “pure” renal revascularization techniques.

Finally, the introduction of newer antihypertensive agents may have some impact on the progression of disease. In short-term studies, dihydropyridine calcium channel blockers have been shown to greatly reduce blood pressure with minimal impairment of renal function in the patients with renovascular disease [32]. The long-term benefits of these agents are unknown. However, the use of ACE inhibitors is controversial. In patients with bilateral renal artery stenosis, treatment with ACE inhibitors can lead to sudden and dramatic increases in serum creatinine. The acute changes are by-and-large reversible, but cases of significant renal impairment have been reported.

In summary, an aggressive approach to revascularization should be pursued. Medical therapy alone in patients with physiologically significant renal artery stenosis will place

them at increased risk for disease progression and worsening renal function. Surgical revascularization still appears to be superior to percutaneous approaches in all but the straightforward main renal artery atherosclerotic and FMD patients. The outcomes and durability of primary PTA and stent placement in ostial atherosclerotic disease remain to be delineated in a large, randomized, prospective trial. Until then it can only be considered as an option to use in the setting of restenosis, poor immediate results, or technically difficult cases. Also, the potential impact that stent placement will have on future surgical revascularization options cannot be discounted. There is still room for improvement in technical designs of stents and their delivery systems that may impact on the viability and durability of this procedure as compared to surgery. The importance of a team approach including a nephrologist, interventional radiologist, and vascular surgeon all aware of the various issues addressed in this chapter and communicating with each other cannot be overemphasized in providing the patient with the highest quality care available.

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Secondary Nonrenal Hypertension

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Secondary hypertension is responsible for < 10% of cases of adult hypertension. The suspicion of a secondary cause should be heightened whenever the clinical picture or response to treatment is not typical of those of essential hypertension [1]. The more atypical the picture is, the higher the suspicion of secondary hypertension should be (Table 1). Clues for the presence of secondary hypertension should be sought in the original evaluation of all hypertensive subjects and during the course of treatment. At a minimum, a urinalysis and potassium (K^+), calcium (Ca^{2+}), and creatinine levels should be done on any patient with confirmed hypertension before treatment is initiated. A detailed history of medicinal and recreational drug use is of utmost importance because many of these substances are known to cause blood pressure elevation [2]. A family history of childhood hypertension, renal disease, pheochromocytoma, endocrinopathies, or hypokalemia may be an important clue to the presence of secondary hypertension.

Table 1. The typical picture of essential hypertension.

- Age of onset 25 – 55, older for isolated systolic HTN
- Asymptomatic
- Mild-to-moderate in severity (< 180/110)
- Lack of grade III or IV retinopathy
- Urinalysis, renal function, and potassium are normal
- Controllable with nonpharmacological measures and up to 3 drugs at maximum doses

In some instances essential and secondary hypertension could coexist, and the removal of the secondary cause (such as excessive alcohol consumption) leads to easier control of the essential component. Removing the cause in correctly diagnosed secondary hypertension leads to normalization of the blood pressure unless there is another coexisting factor, or when the secondary hypertension has been long lasting and already caused irreversible damage to the cardiovascular bed and the kidneys.

Mineralocorticoid Hypertension and Liddle Syndrome

Normal Physiology. The activation of the renin-angiotensin system leads to the production of angiotensin (Ang) II which, among other things, binds to a membrane receptor in the zona glomerulosa of the adrenal cortex leading to a series of reactions that end with aldosterone biosynthesis (Figure 1). Aldosterone acts on the distal tubules and cortical collecting ducts of the kidney by occupying an intracellular receptor, the mineralocorticoid or type I receptor, leading to an increase in the number of sodium channels that

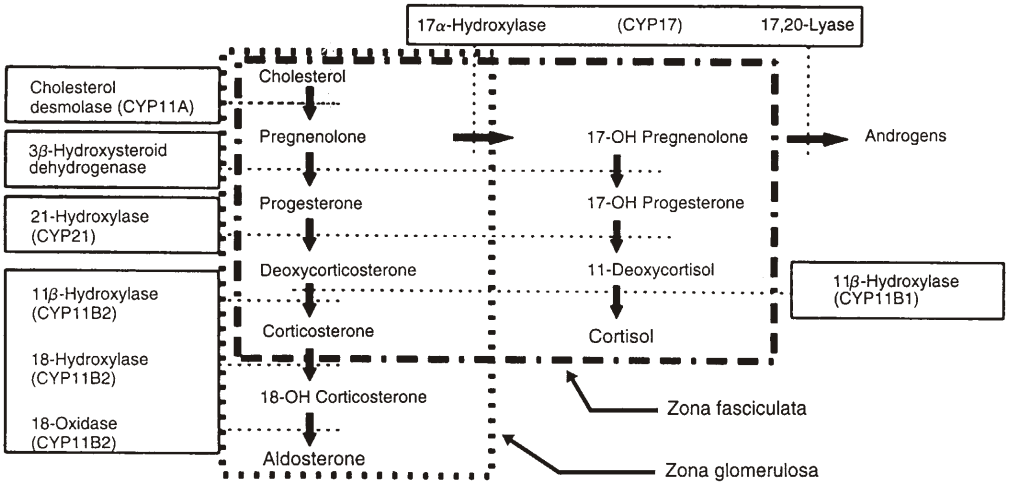

Figure 1. Pathways of adrenal steroid biosynthesis. The conversions occurring in the zonae glomerulosa and fasciculata are marked by broken rectangles. The enzymes responsible for each biosynthetic step are listed in the surrounding boxes. The enzyme CYP11B2 (aldosterone synthase) mediates the last three steps in aldosterone biosynthesis. Deficiencies of CYP11B1 and CYP17 lead to the hypertensive forms of congenital adrenal hyperplasia. Adapted from [3].

are open in the apical membranes of the epithelial cells. Aldosterone also increases potassium conductance into the tubular lumen through specific channels. At the basolateral membrane, aldosterone increases the synthesis of Na^+-K^+-ATPase. The final result is sodium reabsorption and potassium secretion [3].

Under normal circumstances, cortisol is more abundant in the circulation than aldosterone and is capable of binding the mineralocorticoid receptors. However, cortisol is prohibited from activating these receptors because the enzyme 11 -hydroxysteroid dehydrogenase 2 in the endoplasmic reticulum of cells that have mineralocorticoid receptors converts cortisol into the inactive metabolite cortisone (Figure 2) [4].

Mineralocorticoid hypertension and Liddle syndrome share in their pathogenesis an inappropriate increase of sodium (Na^+) reabsorption and potassium and hydrogen ion secretion by the epithelial cells lining the distal tubules and collecting ducts. Hypertension, hypokalemia, and metabolic alkalosis are typical, but the serum potassium might be normal. This group of disorders is caused by one of three mechanisms:

- an excessive production of aldosterone or another substance capable of activating the mineralocorticoid receptor,
- a relative or absolute deficiency of 11 -hydroxysteroid dehydrogenase 2, allowing cortisol to act as a mineralocorticoid (the syndrome of apparent mineralocorticoid excess (AME)), or
- an abnormal Na^+ channel that fails to close in response to deactivation of the mineralocorticoid receptor (Liddle syndrome).

Diagnosis. The usual clue to the diagnosis of mineralocorticoid hypertension is the presence of unprovoked hypokalemia. The workup starts by evaluating renal potassium

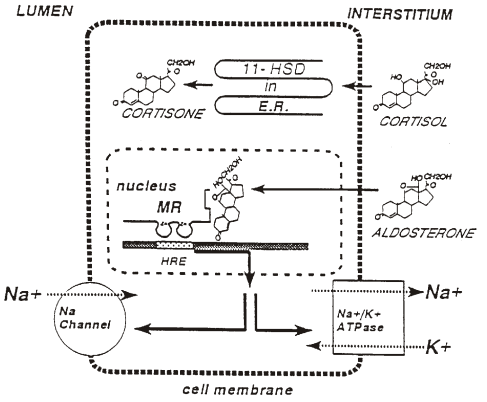

Figure 2. A cell in a renal cortical collecting duct. Aldosterone occupies nuclear receptors (MR) that bind to hormone-response elements (HRE) leading to increased activities of apical sodium channels and the basolateral NA, K-ATPase. The net result is resorption of sodium and excretion of potassium. 11 -hydroxysteroid dehydrogenase, shown in the top, converts the cortisol entering the cell into cortisone, prohibiting it from activation MR. Inappropriate Na^+ reabsorption occurs if there is 1) a defect in the sodium channel (Liddle syndrome), 2) excessive production of mineralocorticoids or 3) insufficient activity of 11-HSD. Adapted from [9].

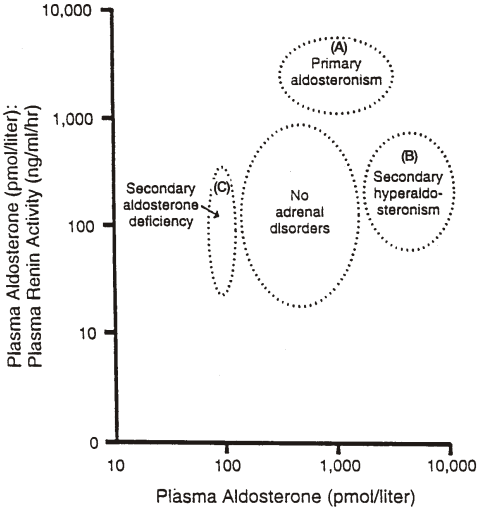

Figure 3. Relation of plasma aldosterone concentration to the ratio of plasma aldosterone to plasma renin activity in mineralocorticoid hypertension. To convert values of plasma aldosterone from ng/dl to pM/l multiply by 27.7. Adapted from [3].

excretion while the patient is hypokalemic. Decreased distal delivery of Na^+ and water may lead to diminished potassium excretion; thus, one has to assure that, at the time of evaluation, Na^+ excretion is 50 mEq/24 hours. Under these circumstances, kaliuria of more than 30 mEq/24 hours, in the absence of diuretic therapy, confirms the diagnosis of a hypokalemic hypertensive syndrome. The next step would be to correct the hypokalemia with potassium chloride supplement and obtain a random ambulatory plasma aldosterone (PA) and plasma renin activity (PRA). From these, a PA/PRA ratio could be calculated. Diuretics, ACE inhibitors, Ang II blockers, -blockers, and possibly calcium channel blockers interfere with these measurements and, according to traditional teachings, should be avoided when these tests are done [5]. Recently, the need to discontinue blood pressure medication has been challenged. The author recommends that at least ACE inhibitors and angiotensin receptor blockers be stopped before testing is done. Spironolactone should not be initiated until these tests are finished. If the patient is already on this drug, it will need to be discontinued for more than a month before renin and aldosterone measurements are done. Plotting the results in the graph in Figure 3 will help in the differential diagnosis and guide further workup [3, 6]. This nomogram is inaccurate in patients with chronic renal failure (CRF).

Primary Hyperaldosteronism

It has been described in all age groups but mostly in the fourth and fifth decades of life.

Hypokalemia is usually the cause for suspecting this diagnosis. The development of a K^+ level below 3 mEq/l during treatment with conventional doses of diuretics, the unresponsiveness of milder degrees of diuretic-induced hypokalemia to potassium supplements, or the addition of potassium-sparing diuretics are also reasons to consider this diagnosis. Hyperaldosteronism should be suspected in patients with resistant or severe hypertension regardless of their potassium levels. About half of the hypertensive patients with unprovoked hypokalemia have primary hyperaldosteronism.

The source of the excess aldosterone is an adrenal adenoma in about one half to two-thirds of cases, bilateral adrenal hyperplasia in the majority of the rest and, rarely, other pathologies, including unilateral adrenal hyperplasia, carcinoma, and ectopic aldosterone-producing tumors [5]. Patients with adenomas tend to be younger at the time of diagnosis and have evidence of more severe disease manifested by higher blood pressure, lower serum K^+, and more profound alkalosis. Most cases are sporadic, but familial forms of both hyperplasia and adenoma exist. Coexistence of primary aldosteronism with pheochromocytoma and fibromuscular hyperplasia of the renal artery has been rarely described.

Hypokalemia, metabolic alkalosis, and, at times, hypomagnesemia are the result of increased K^+, hydrogen (H^+), and magnesium (Mg^{2+}) secretion in exchange of the Na^+ being reabsorbed. Hypokalemia leads to weakness and renal resistance to antidiuretic hormone (ADH) with resultant polyuria and polydipsia. The loss of free water can lead to borderline hypernatremia. Some patients are tachycardic and have signs of a hyperkinetic circulatory state.

Normokalemic primary hyperaldosteronism was reported to be present in 7% to as high as 50% of cases. It is more often associated with hyperplasia than adenoma and may become hypokalemic in the course of the disease, either spontaneously or following the use of diuretics. The search for primary hyperaldosteronism need not be done when the serum potassium is normal except in the cases of resistant or severe hypertension or if a familial form is suspected. Rare cases of normotensive hyperaldosteronism have been described.

Diagnosis. As discussed previously, unprovoked hypokalemia is usually the clue to considering the diagnosis of primary hyperaldosteronism. The workup should start as explained above. At times the picture is very clear, but usually further testing is needed. The purpose of these tests is to try to document that PRA is not stimulable by procedures such as upright posture and use of diuretics and that aldosterone level is not suppressible by procedures such as volume expansion. Many of these tests have been described. Documentation of low PRA (< 1.0 ng/ml/hour) after 2 hours of upright posture with elevated aldosterone levels of > 10 ng/dl following the administration of 2 l of normal saline over 4 hours are usually diagnostic. Aldosterone values between 6 and 10 ng/dl fall in the gray zone and are sometimes seen in hyperplasia. Normal subjects suppress aldosterone levels to < 5 ng/dl. An elevated 24-hour urinary aldosterone level (> 14 g/24 hours) while the patient is on a high sodium diet (as documented by > 250 mEq of Na excretion in the collection) is useful. Failure to suppress aldosterone level after oral captopril is an alternative to salt loading.

Once primary aldosteronism is diagnosed, differentiation between adenoma and hyperplasia needs to be made. This is often difficult, and none of the numerous techniques has a discriminatory power of 100%. The upright posture test, 18-hydroxycorticosterone (18-

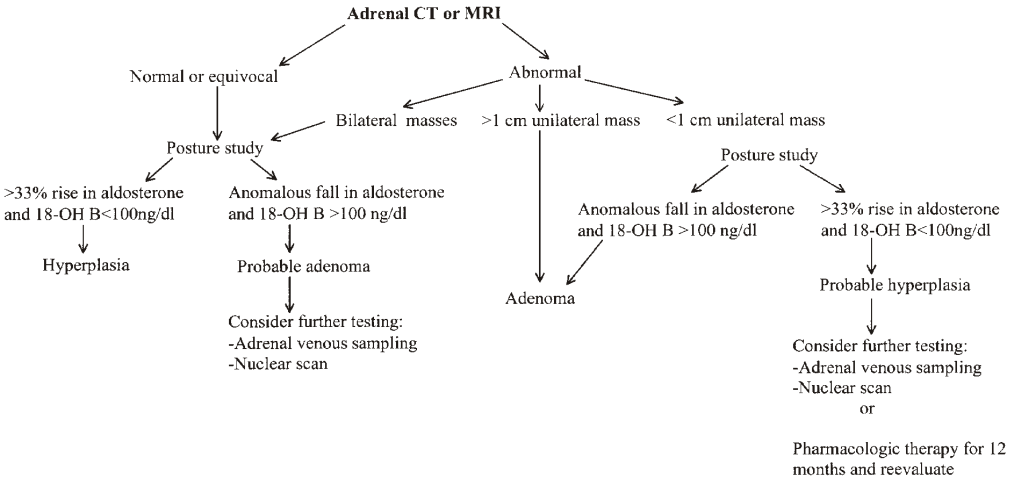

Figure 4. A suggested algorithm for the differentiation between aldosterone-producing adenomas and hyperplasias. 18-OHB ist 18-OH corticosterone. Adapted from [7].

OHB) levels, adrenal venous aldosterone measurements, iodocholesterol nuclear scanning with dexamethasone and adrenal computed tomography (CT) all have good discriminatory power. All adenomas 1.5 cm in diameter, 60% of those between 1 and 1.4 cm, and rarely adenomas measuring < 1 cm can be diagnosed with CT. A suggested scheme is shown in Figure 4.

The 4-hour upright test is based on the concept that adenomas as opposed to hyperplasias do not respond to postural-induced stimulation of the renin-angiotensin system. The sensitivity and specificity of this test for detecting an adenoma are about 80%. 18-OHB is a precursor of aldosterone. Its basal level is usually > 100 ng/dl in adenomas and < 60 ng/dl in hyperplasia. Adrenal venous plasma aldosterone is an invasive and skill-requiring procedure with success rates in some expert hands of no more than 65%. Complications including venous thrombosis and adrenal insufficiency secondary to radiocontrast extravasation into the adrenals can occur. Normal adrenal venous concentration is 200 – 600 ng/dl. In adenomas the ratio of ipsilateral to contralateral aldosterone is usually > 10 : 1. To assure correct catheter placement, adrenocorticotropic hormone (ACTH)-stimulated cortisol levels should be symmetrical. Nuclear imaging, where available, is less invasive. NP-59 scanning is reported to be more advantageous than iodocholesterol. The test is best done with dexamethasone suppression where adenomas remain visible and bilateral hyperplasias fade.

Therapy. Adenomas are best treated surgically. Preoperative therapy with spironolactone may help predict the response to therapy and should ameliorate the hypertension and hypokalemia perioperatively. Postoperatively aldosterone deficiency with hypotension and hyperkalemia may develop but usually resolve within 6 months. In the Cornell series, surgery led to a cure of hypertension in 35% of cases and improvement in 56%. Younger age, lower PRA, and lateralization of aldosterone secretion were associated with higher probability of cure. Enucleation of adenomas, compared to unilateral

adrenalectomy, led in one study to a better reserve adrenocortical function. This is probably of no clinical importance, and the enucleation technique is more complicated. Laparoscopic adrenalectomy is an option that has gained popularity in the recent years and has become the surgical method of choice.

Spironolactone is the treatment of choice for adrenal hyperplasia and in patients with adenomas not treated surgically. Medical management of adenomas has been shown to provide good results and should be considered in patients who are not good surgical candidates, those who elect not to have surgery and whenever differentiation between a hyperplasia and an adenoma is difficult [8]. Doses of 50 – 200 mg/day are used; salt restriction should enhance the response. Other potassium sparing diuretics such as triamterene or amiloride could be used in patients intolerant to spironolactone. Thiazide diuretics, -blockers and calcium channel blockers could be used in addition to spironolactone in the patient that require combination therapy to control their blood pressure.

Glucocorticoid-remediable Aldosteronism (GRA)

GRA is a rare autosomal dominant form of hyperaldosteronism with bilateral hyperplasia characterized by the production of aldosterone in the zona fasciculata and suppressibility of the hyperaldosteronism by glucocorticosteroids [9]. The disease is also called glucocorticoid-suppressible hyperaldosteronism and dexamethasone-suppressible hyperaldosteronism.

Cortisol and aldosterone syntheses require 11 -hydroxylation of steroid intermediates. These steps are normally catalyzed by different isoenzymes, respectively termed steroid 11 -hydroxylase (CYP11B1) in the zona fasciculata and aldosterone synthase (CYP11B2) in the zona glomerulosa. The latter isoenzyme also catalyzes the subsequent 18-hydroxylation and 18-oxidation steps required for aldosterone synthesis (Figure 1).

Subjects with GRA have been shown to have 3 rather than 2 CYP11B genes. The extra gene, located between the other two, is chimeric and contains the regulatory region of the enzyme that promotes the conversion of deoxycortisol to cortisol (11 -hydroxylase or CYP11B1) and the coding sequences of the aldosterone synthase gene (CYP11B2). The former confers a zona fasciculata location and ACTH sensitivity and the latter aldosterone production [9].

Hypertension in most instances occurs in the first two decades of life. Many affected patients, diagnosed by genetic testing, are even normotensive. Serum K^+ is normal in more than half of the cases, but these subjects tend to develop pronounced hypokalemia with the use of diuretics. The high prevalence of normokalemia is thought to be due to a diurnal decline of aldosterone that follows ACTH level. Hemorrhagic strokes and ruptured intracerebral aneurysms are common. Screening for these aneurysms with magnetic resonance angiography is recommended in all patients. Levels of the urinary hybrid steroid 18-oxocortisol are elevated and could be used to make the diagnosis. In a study of 15 patients with this syndrome, all had values of > 40 /g of creatinine. The highest value in 11 normals was 17.4 /g of creatinine. 18-hydroxycortisol levels are also elevated. Genetic testing is available and preferable. The treatment of this condition is the use of glucocorticoids to suppress ACTH production and thus aldosterone production in the zona fasciculata. The starting dose in adults is 1 – 2 mg of dexamethasone daily. This usually

leads to normalization or at least improvement of the blood pressure. When 18-oxocortisol studies and genetic testing are not available, the hypotensive and chemical responses to 0.5 mg of dexamethasone 4 times daily could be used as a diagnostic test.

Tumors Producing Mineralocorticoids Other Than Aldosterone

Tumors producing deoxycorticosterone or 21-deoxyaldosterone rather than aldosterone have been described. The picture is that of mineralocorticoid excess without elevation of the serum aldosterone. These tumors are usually malignant and are easily detectable by CT because of their size. Androgen and estrogen secretion is common.

The Syndrome of Cortisol Resistance

In this familial disease there is partial cortisol resistance with resultant ACTH-induced increased synthesis of steroids with mineralocorticoid activity, androgens, and cortisol. Patients usually have mineralocorticoid hypertension, symptoms of androgen excess, but no cushingoid features. The clinical presentation is extremely variable [10].

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia comprises a group of autosomal recessive disorders that result from deficiencies in enzymes necessary in the synthesis pathways of adrenocortical hormones. Manifestations are the result of inadequate levels of the end products of steroid synthesis, especially cortisol, and the overproduction, in the zona fasciculata, of the precursor steroids proximal to the enzymatic block (Figure 1). Most cases of congenital adrenal hyperplasia are normotensives, but two uncommon syndromes – 11 -hydroxylase deficiency and 17 -hydroxylase deficiency – are often associated with hypertension and hypokalemia. Aldosterone levels are typically low. In both conditions, glucocorticoid therapy, by suppressing ACTH production, corrects the metabolic abnormalities and the hypertension [9].

11 -hydroxylase (CYP11B1) deficiency occurs in about 1 in 200,000 births. Hypertension is present in two-thirds of patients. The onset is often in the first few years of life, and the incidence of end-organ damage is high. Hypokalemia is not common. The ability to synthesize aldosterone is unimpaired, but renin and aldosterone levels are both suppressed. Deoxycorticosterone levels do not correlate well with blood pressure and other substances, including some metabolites of deoxycorticosterone, seem to play a role in the pathogenesis of hypertension. Accumulation of adrenal androgens leads to signs of masculinization at birth and rapid somatic growth during childhood. Levels of deoxycorticosterone and 11-deoxycortisol in the serum and their tetrahydrometabolites in the urine are elevated. Genetic analysis has thus far identified 20 different mutations in the CYP11B1 gene in patients with classical forms of this disorder [9].

17 -hydroxylase (CYP17) deficiency is less common than 11 -hydroxylase (CYP11B1) deficiency. Symptoms of adrenal insufficiency are lacking because corticosterone is a glucocorticoid agonist. Excessive production of deoxycorticosterone leads to

hypertension. The production of sex hormones is impaired. The disease is usually recognized at the age of puberty when symptoms of hypogonadism, primary amenorrhea, and sexual infantilism in females and pseudohermaphroditism in males are noted. Growth is usually not impaired. Elevated progesterone levels and near absence of 17 -hydroxyprogesterone and androgens in the serum and 17-ketosteroids in the urine are diagnostic. Mutations in the CYP17 gene have been identified in many patients with this disorder [11].

Hypokalemic Hyperreninemic Hypertension

In this group of disorders, both the renin and aldosterone are elevated. In some instances, such as diuretic-induced hypokalemia, hypertension and hypokalemia are caused by different mechanisms. In other instances, both hypokalemia and hypertension are a result of stimulation of the renin-angiotensin axis.

Renin-producing Tumors

Renal and extrarenal renin-producing tumors have been described infrequently in the literature [12]. Renin and more impressively prorenin levels are usually extremely high, and the hypokalemia could be severe. Hyponatremia and heavy proteinuria have sometimes been described. Tumors of the juxtaglomerular apparatus, Wilms tumors, rare cases of renal cell carcinomas, and few extrarenal malignancies have been the source of the renin excretion. Renal angiogram is usually needed to rule out renovascular hypertension, which can rarely cause a similar metabolic picture [13]. CT is useful for tumor localization. The hypertensive hypokalemic syndrome responds to treatment of the tumor and ACE inhibitors.

Diuretic-associated Hypokalemic Hypertension

The coexistence of essential hypertension and diuretic-induced hypokalemia is the most common cause of hypokalemic hypertension. In the majority of cases the diagnosis is straightforward. Occasionally a patient with surreptitious diuretic abuse may pose a diagnostic challenge. The syndrome of surreptitious diuretic abuse is classically classified as a cause of normotensive hypokalemia when it needs to be differentiated from Bartter syndrome. However, because essential hypertension is common in the general population and because hypertensives may have easier access to diuretics, it could be seen in association with essential hypertension. Urinary K^+ excretion is elevated, but if the patient stops the diuretic before the urine collection it could be low as a result of the body's appropriate response to conserve K^+. Screening for the presence of diuretics in the urine is available.

Cortisol-induced Mineralocorticoid Excess

This is a group of disorders characterized by excess mineralocorticoid activity exhibited by cortisol. The renal isoform of the enzyme 11 -hydroxysteroid dehydrogenase (11 -HSD2) is either congenitally deficient, chemically inhibited, or overwhelmed by large amount of cortisol, allowing this substance to activate the mineralocorticoid receptors in the distal tubules (Figure 2). In all

these disorders aldosterone, deoxycorticosterone levels, and PRA are low [4].

The Syndrome of Apparent Mineralocorticoid Excess (AME)

In the more common congenital form of AME (type 1), there is a mutation in the gene for the kidney isoform of 11 -hydroxysteroid dehydrogenase (the NAD-dependent isoform) located in chromosome 16q22. The disease is inherited in an autosomal recessive manner. The ratio of the cortisol metabolites tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone, normally about 1 is 8. Clinical manifestations include hypertension and hypokalemia during childhood, intrauterine growth retardation, and failure to thrive. The administration of dexamethasone, by suppressing cortisol production, will correct the hypokalemia, but antihypertensives are often still needed to control the blood pressure. Genetic testing is available. The diagnosis is usually made in children and young adults.

11 -hydroxysteroid dehydrogenase activity is inhibited by licorice or similar compounds. The inhibiting chemical in licorice is a steroid named glycyrrhetinic acid. It works both competitively and by reducing gene expression. Flavonoids present in grapefruit juice have been shown experimentally to inhibit 11 -hydroxysteroid dehydrogenase. The clinical importance of this finding is unknown. Licorice is present in some confectionery items, chewing tobacco, chewing gum, and some drinks, pastis in France and ark al-soos in the Middle East. Carbenoxolone, an antiulcer medication, has a chemical structure similar to that of glycyrrhetinic acid and can cause the same syndrome. The hypertension and hypokalemia should resolve within weeks after the discontinuation of the offending agent. Patients with chronic renal failure, especially those with hypertension, have evidence of decreased activity of 11 -hydroxysteroid dehydrogenase, and this may be one of the mechanisms in the pathogenesis of renal hypertension.

A rarer syndrome called AME type 2 was described. As opposed to AME type 1, the ratio of the cortisol metabolites tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone is normal. Some research has suggested that the hypertensive syndrome seen with the carbenoxolone is an acquired form of this disorder. Explanations of how AME type 2 differs from AME type 1 are discussed elsewhere [4].

Cushing Syndrome

In Cushing syndrome, which is caused by ectopic production of ACTH, and less commonly in other forms of Cushing syndrome, the amount of cortisol produced could overwhelm 11 -hydroxysteroid dehydrogenase, and enough cortisol at the levels of the distal renal tubules will be left to exert mineralocorticoid activity. Evidence also indicates that in this condition there is inhibition of 11 -hydroxysteroid dehydrogenase, possibly by ACTH. More commonly the hypertension of Cushing syndrome is not hypokalemic and is discussed in another chapter.

Liddle Syndrome

In Liddle syndrome the collecting tubule Na^+ channel, which is the path Na^+ takes when entering from the tubule into the cell, fails to close in response to aldosterone suppression caused by volume expansion. The

Table 2. The differential diagnosis of mineralocorticoid hypertension.

Renin Aldosterone Profile *	Syndrome	Steroids Involved	Suppressible by	Genetic Defect	Diagnostic Clues
Zone A	Aldosteronoma	Aldosterone	Surgery	No	See Figure 2
	Idiopathic primary aldosteronism	Aldosterone		No	See Figure 2
	GRA	Aldosterone	Dexamethasone	Yes (AD)	Elevated 18-oxocortisol, 18-hydroxycortisol
Zone B	Renovascular hypertension	Aldosterone	Surgery or angioplasty	No	Renal arteriogram and other tests
	Renin producing tumors	Aldosterone	Surgery	No	Imaging studies, elevated prorenin
	Diuretic abuse	None	Discontinuation	No	History, urine screening for diuretics
Zone C	AME type I	Cortisol	Dexamethasone	Yes (AR)	Intrauterine growth retardation, failure to thrive, elevated (THF + Allo THF)/THE
	Licorice abuse	Cortisol	Discontinuation	No	History, urine screening for glycyrrhetinic acid
	Cushing's syndrome	Cortisol	Surgery, ketoconazole, mitotane	No	Very high cortisol, tumor
	CAH: CYP 11B deficiency	DOC 11-deoxycortisol	Dexamethasone	Yes (AR)	Virilization, high DOC and 11-deoxycortisol, high 17-ketosteroids
	CAH CYP 17 deficiency	DOC 19-nor-DOC	Dexamethasone	Yes (AR)	Hypogonadism, high progesterone and low 17-ketosteriods
	Syndrome of cortisol resistance	DOC	Dexamethasone	Yes (AD)	High cortisol and ACTH, androgen excess, no cushingoid features
	DOC-producing tumors	DOC	Surgery	No	Imaging studies, elevated DOC
	Liddle syndrome	None	Amiloride, triamterene	Yes (AD)	Lack of response to spironolactone, normal cortisol

Adapted from Vallotton MB, Part II, 1996 [15]
* See Figure 3, AD = Autosomal dominant, AR = Autosomal recessive, THF = Tetrahydrocortisol, Allo-THF = Allotetrahydrocortisol, THE = Tetrahydrocortisone, CAH = Congenital adrenal hyperplasia, DOC = Deoxycorticosterone

disease is transmitted in an autosomal dominant fashion. It is caused by mutations in the carboxyl-terminus of the beta or gamma subunits of the renal epithelial Na^+ channel's gene.

Liddle syndrome usually presents itself in childhood with hypertension, hypokalemia, low renin and aldosterone, and normal cortisol levels. Genetic testing of relatives of index cases has shown that the hypertension could be mild and not apparent until adulthood and that hypokalemia is often absent, suggesting that this disease may be underdiagnosed [14]. Liddle syndrome was originally described in whites and Orientals but black individuals were recently found to have it.

The potassium-sparing diuretics triamterene and amiloride directly close the sodium channels and are used in the treatment of Liddle syndrome. Spironolactone is ineffective because the increase of sodium channel activity in this disorder is independent of aldosterone. This feature could help diagnostically. Failure to respond to dexamethasone-induced ACTH suppression distinguishes this syndrome from AME.

Table 2 summarizes features that might be helpful in the differential diagnosis of mineralocorticoid hypertension [15].

Pheochromocytoma

Pheochromocytomas are catecholamine-secreting tumors that arise from neuroectodermal chromaffin cells, which are part of the adrenergic system. Their exact prevalence is unknown, but they are thought to be responsible for less than 0.1% of all cases of hypertension. About 90% of tumors are located in the adrenal medulla. The rest occur in other sites in the abdomen and pelvis such as the organ of Zuckerkandl, paraganglia chromaffin cells, and the urinary bladder, and < 2% above the diaphragm in a paraspinal location, the pericardium, the neck, base of the skull, and other rare sites. The typical pheochromocytomas are sporadic, singular, and benign but some violate one or more of these rules. They occur at any age but more commonly in the fourth and fifth decades. They are more common in females except in the pediatric age group.

Clinical Manifestations. The clinical manifestations of pheochromocytomas result mainly from excess circulating catecholamines and complications of hypertension. Occasionally the secretion of a variety of peptides, local effect of the tumor, and the presence of a coexisting syndrome contribute to the picture. Due to the variation of the rate of catecholamine secretion and its dependence on many exogenous and endogenous stimuli, symptoms and signs tend to be paroxysmal. The frequency of the attacks varies from several per day to one every few months. They typically last less than an hour, but the duration also varies. The onset is abrupt and the resolution is slow.

At least two of the symptoms from the classical triad of headache, tachycardia, and sweating are present in almost all patients with pheochromocytoma. Pallor, dizziness, acute anxiety, tremulousness, pain in the chest and other sites, nausea, vomiting, constipation, symptoms of ischemic bowels, symptoms of dilated cardiomyopathy, weight loss, fever, and other symptoms could also be present. Hyperglycemia is a common laboratory finding in pheochromocytoma. Hypokalemia, hypercalcemia, and lactic acidosis are rarely encountered.

The hypertension in pheochromocytoma is paroxysmal in about 50% of cases and persistent in the other half. Even in this group blood

pressure tends to fluctuate widely. Rarely, patients with predominantly epinephrine-secreting tumors have hypertension alternating with hypotension. Orthostatic hypotension with tachycardia can occur and is attributed to desensitization of the adrenergic receptors and volume depletion.

Some drugs such as -blockers may precipitate a hypertensive attack. This reaction is due to the blockade of the vasodilatory peripheral -receptors with unopposed alpha stimulation. Stressors such as intubation, anesthesia, surgery, and trauma may cause a severe pressor reaction. Unexplained circulatory shock, especially perioperatively, during pregnancy and delivery, and following administration of phenothiazines, may be seen. Bladder pheochromocytomas are associated with painless hematuria, and attacks could be precipitated by bladder distension or micturition.

Occasionally, pheochromocytomas secrete some substances such as vasoactive intestinal peptide (VIP), serotonin, calcitonin, erythropoietin, adrenocorticotropic hormone, parathyroid hormone (PTH)-related protein, and renin leading to some unusual manifestations. Cholelithiasis, for some unexplained reason, is reported to be common.

Two forms of multiple endocrine neoplasia (MEN-2A and MEN-2B) are, in about 40% of cases, associated with pheochromocytoma. Both are inherited in an autosomal dominant fashion. MEN-2A includes medullary thyroid carcinoma or C-cell hyperplasia and hyperparathyroidism, and MEN-2B includes medullary thyroid carcinoma in almost all cases, mucosal neuromas of the lips and tongue, thickened corneal nerves, alimentary tract ganglioneuromatosis, megacolon, and marfanoid habitus. Pheochromocytomas associated with MEN are bilateral in 30% of cases. Malignant disease in familial forms of pheochromocytoma is rare.

Pheochromocytoma is also a feature of von Hippel-Lindau (vHL) disease, which also includes retinal angiomas, hemangioblastoma of the central nervous system (CNS), renal cysts and carcinoma, pancreatic cysts, and epididymal cystadenoma. Bilateral disease is common. Extraadrenal pheochromocytomas are more frequently vHL disease compared to sporadic cases and those associated with MEN-2. Patients with neurofibromatosis type 1 (NF1), tuberous sclerosis (TS), familial carotid body tumors and Sturge-Weber syndrome have increased prevalence of pheochromocytoma.

In a study from Germany [9], 23% of 82 unselected patients with pheochromocytoma were found to be gene carriers of MEN-2 or vHL disease. The authors of this study recommended that every patient with a pheochromocytoma be screened for both MEN-2 and vHL by the pentagastrin test, measurement of serum PTH, ophthalmoscopic examination, MRI of the brain, CT of the abdomen, and ultrasound of the testicles. First-degree relatives of patients with one of these syndromes and of patients with multifocal pheochromocytomas should have pheochromocytoma ruled out regardless of their symptomatology [16].

Diagnosis. Pheochromocytoma should be suspected in patients with severe or refractory hypertension, when one or more of the features detailed above are encountered in a hypertensive patient, or when an adrenal mass is found incidentally in an imaging study. Patients diagnosed with one of the above hereditary disorders and their family members should be screened periodically for the disease. Genetic testing for the RET oncogene of MEN-2 and the von Hippel-Lindau tumor suppressor gene could be done at some research laboratories.

Many conditions may mimic pheochromocytomas, including hyperkinetic hyperten-

Table 3. Drugs and substances that may interfere with the measurements of urinary catecholamines and their metabolites.

Increase Apparent Value	Decrease Apparent Value
Benzodiazepines	Clofibrate
Catecholamines and drugs containing catecholamines	Disulfiram
Chlorpromazine	Ethanol (VMA levels)
Erythromycin	Fenfluramine (large doses), -methyltyrosine
Ethanol (catecholamine and metabolite levels)	MAO inhibitors (VMA levels)
Isoprenolol (Isoproterenol)	Methylglucamine (in renovist. renografin, etc.)
Labetalol	
Levodopa	
MAO inhibitors (metanephrine levels)	
Methyldopa	
Nalidixic acid	
Other fluorescent substances (e.g., quinine, quinidine, bile in urine)	
Rapid clonidine withdrawal	

Manger WM, Gifford RW 1995 Pheochromocytoma: a clinical overview. Adapted from [17], p. 2237.

sion, hyperthyroidism, panic attacks, hypoglycemic reactions, menopause, abuse of street drugs including cocaine and amphetamines, use of medications such as phenylpropanolamine or -agonists, the concomitant use of a monoamine oxidase inhibitor (MAOI), tyramine-containing foods, and clonidine and -blocker withdrawal.

Many tests for diagnosing pheochromocytoma are available. The low pretesting prevalence of pheochromocytoma, even in patients with suggestive features, makes the positive predictive value of highly specific tests also low. The search for pheochromocytoma remains very important due to the severe consequences of missing the diagnosis. The recently developed test for measurement of plasma-free metanephrines, due to its very high sensitivity of 99% and a high speceficity of 89% (at upper reference limits are 0.66 pmol/ml for plasma normetanephrine and 0.30 pmol/ml for metanephrine) should be the diagnostic test of choice [18]. The high sensitivity of the test is due to the fact that free metanephrines, as oppesed to catecholamines, are released continuously from the tumor into the blood. The sensitivity of other tests including urinary studies and plasma catecholamines is much lower. A normal level of both metanephrine and normetanephrine rules out the diagnosis. Patients who have normetanephrine levels that exceed 2.5 pmol/ml or metanephrine levels above 1.5 pmol/ml are confirmed to have pheochromocytoma. If levels are high but neither exceeds these values, then the test should be repeated and a normal value of both rules out the diagnosis. The rest of patients should have a

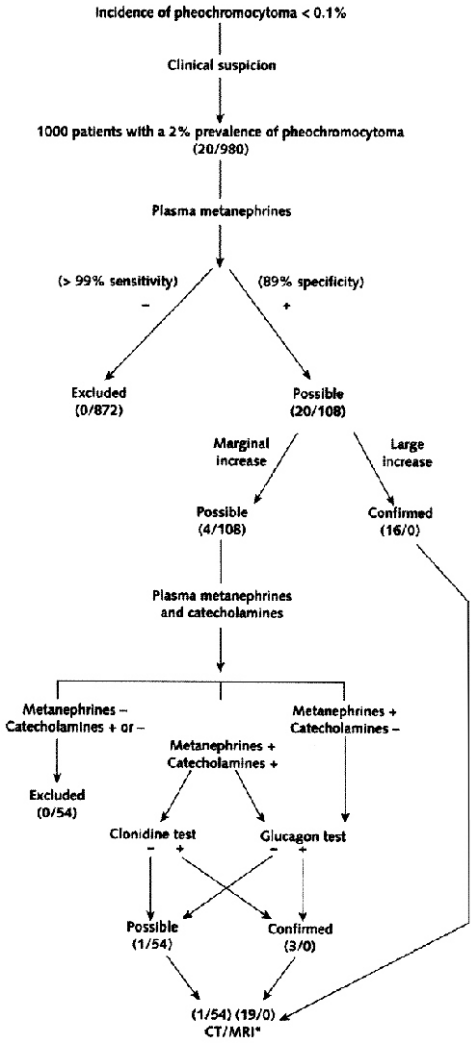

Figure 5. A suggested algorithm for the workup and localization of pheochromocytoma. Adapted from [18]. Used with permission.

diagnostic workup as shown in Figure 5. Plasma metanephrine levels are elevated in monoamine oxidase deficiency. Caffeine and acetaminophen should be avoided prior to testing. Measurement of total plasma catecholamine levels (epinephrine + norepinephrine), requires that blood be drawn via a previously inserted indwelling catheter after the patient has rested in a supine position for 30 min. If plasma tests are not available, urinary tests could be done instead; these tests suffer from low sensitivity making ruling out the diagnosis a difficult task. A combination of these tests increases the sensitivity at the expense of specificity. Many drugs and substances may interfere with the measurement of catecholamines and their metabolites (Table 3).

The clonidine suppression test is used to differentiate between pheochromocytomas and other conditions associated with elevated catecholamines, such as neurogenic hypertension. By suppressing the sympathetic nervous system, clonidine reduces the norepinephrine level by 50% or to a normal value in neurogenic hypertension, but not in patients with pheochromocytoma. -blockers should be discontinued at least 2 days before testing because they can interfere with the suppression of catecholamine concentration in patients with neurogenic hypertension. Drugs that interfere with catecholamine measurements should also be avoided (Table 3), and other antihypertensive medications should be discontinued at least 12 hours before the test. Volume depletion at the time of the test can lead to profound hypotension, and, if present, it should be treated beforehand. The test consists of obtaining baseline plasma catecholamines as described previously followed by administration of 0.3 mg of clonidine orally and then after 3 hours of bed rest another plasma catecholamine determination. Patients without a pheochromocytoma usually suppress the total catecholamine concentration to < 500 pg/ml.

Rarely, the glucagon stimulation test is required to diagnose a paroxysmally secreting tumor. It consists of obtaining a baseline catecholamine specimen, followed by the administration of 1 mg of intravenous (IV) glucagon and a second measurement 2 min

after the infusion. The diagnosis of pheochromocytoma is made if there is a 3-fold rise in catecholamine levels or if the absolute value becomes > 2000 pg/ml. This test is contraindicated if the blood pressure is > 160/105. Premedication with an $_1$-blocker or nifedipine may prevent a hypertensive response without interfering with the measurements. This test should be done under monitored conditions.

Localization Procedures. A CT or MRI of the adrenal gland and abdomen identify 95% of pheochromocytomas. A high signal intensity on MRI is characteristic. Detecting small tumors by these methods may be difficult but usually is not a problem because pheochromocytomas are generally > 3 cm in size.

When the CT or MRI is negative and the diagnosis is still strongly considered, an ^{131}I metaiodobenzylguanidine (MIBG) radionuclide scan may be done. It concentrates in 85% of the tumors and is helpful in detecting small and extraabdominal pheochromocytomas. False positive results may be seen in neuroblastomas, medullary thyroid carcinomas, carcinoids, and small cell carcinomas of the lung. Calcium channel blockers, labetalol, tricyclic antidepressants, sympathomimetics, and tranquilizers can decrease the sensitivity of the test and thus should be discontinued a week before it is done. MIBG scan can detect metastases in malignant pheochromocytomas.

Other methods that could be used for localization include CT or MRI of the chest, neck, head, and pelvis, cystoscopy, and central venous blood sampling. Care should be taken to avoid precipitating an attack whenever an invasive procedure is planned. Fluorodopamine positron emission tomography (PET) scanning has been recently suggested to be highly sensitive for tumor localization.

Treatment. The treatment of pheochromocytoma should be resection of the tumor. Except in rare emergent situations such as uncontrollable malignant hypertension or a hemorrhagic necrosis of a pheochromocytoma, preoperative preparation with alpha blockade is warranted. Phenoxybenzamine, starting at a dose of 10 mg daily and gradually increasing the dose to control the blood pressure and symptoms, should be used preoperatively. An $_1$-blocker like prazosin may be used instead. Excessive alpha blockade should be avoided because it can lead to orthostatic hypotension. After adequate alpha blockade and if tachyarrhythmias are of concern, then -blockers starting at small doses could be used. Cardioselective -blockers are preferable. Alpha-methyl-para-tyrosine reduces tumor stores of catecholamines and should be used preoperatively. Increased salt intake together with pharmacological measures should be initiated two weeks before surgery.

An abdominal approach is preferable to ensure adequate visualization, but if the tumor has been localized by CT or MRI then a flank incision or even a laparoscopic approach may be used. Intraoperative hypertension is treated by phentolamine or nitroprusside. Transient hypoglycemia may occur postoperatively, and it is caused by a rise in insulin level.

Patients with malignant tumors are treated by surgical debulking. Residual tissue may be treated by conventional radiotherapy, chemotherapy, metyrosine, and alpha and beta blockade. The 5-year survival is 35 – 50%. Radiofrequency ablation has been used recently to treat metastatic disease.

Hypertension in Hypothyroidism and Hyperthyroidism

Thyrotoxicosis is associated with an increase of cardiac output and blood volume and a decrease in systemic vascular resistance. A widened pulse pressure and an increase in systolic blood pressure are thus expected, and treatment to a euthyroid state usually leads to normalization of these abnormalities. This diagnosis should be suspected in young patients with systolic hypertension, those with a hyperdynamic state, and those with other suggestive clinical features.

In hypothyroidism the hemodynamic profile is the exact opposite to that seen in hyperthyroidism. Hypertension is seen in as many as 50% of patients, and narrow pulse pressure is characteristic. Depressed glomerular filtration rate (GFR), presumably secondary to decreased renal perfusion, is occasionally seen. Thyroid replacement therapy improves or cures the hypertension [19].

Hypertension in Primary Hyperparathyroidism

The association between hyperparathyroidism and pheochromocytoma was discussed earlier. Even in isolated hyperparathyroidism, the prevalence of hypertension is double that seen in the general population. The nature of this association is not clear. Some of these patients may have coexisting essential hypertension. In some experimental models, hypercalcemia can cause vasoconstriction and an increase in cardiac output, but other factors seem to play a role. Elevated PRA and aldosterone levels in hypertensive hyperparathyroid patients with a significant decrease after parathyroidectomy have been reported.

The diagnosis is suspected when hypercalcemia, spontaneous or after the use of thiazide diuretics, is discovered or during the workup of renal stone disease. Studies on the response of the hypertension to surgical parathyroidectomy have shown conflicting results, with some reporting improvement and others no response or even worsening. The presence or lack of hypertension should not be used as a factor when deciding whether to do a parathyroidectomy.

Hypertension in Acromegaly

Hypertension in acromegaly is present in 40% of cases. High levels of growth hormone lead to sodium retention, cardiomegaly, and an increase in cardiac output. Coarse facial features, large hands, carpal tunnel syndrome, coronary artery disease (CAD), and insulin resistance are some of the clinical features. The diagnosis is made by finding high levels of growth hormone during a glucose tolerance test or elevated insulin-like growth factor I (IGF-I).

Hypertension in Neurological Disorders

Considering the essential role the nervous system plays in the control of blood pressure, it is rather surprising that hypertension in neurological diseases is not that common. Severe

Table 4. Exogenous substance-induced hypertension (Part 1).

Ingredients	Common Use/Abuse	Notes
Steroids		
Glucocorticoids	Replacement therapy and symptomatic treatment of various diseases	Dose-dependent, sustained increase mainly in systolic BP
Mineralocorticoids		
Black licorice	Candy, chewing gum, liquor	Dose-dependent, sustained increase in BP mimicking primary hyperaldosteronism characterized by hypokalemia metabolic alkalosis, and suppressed plasma renin activity and aldosterone levels
Carbenoxolone	Ulcer medication	
9 -fluoroprednisolone	Skin ointments, antihemorrhoid cream	
9 -fluorocortisol	Ophthalmic drops and nasal sprays	
Ketoconazole	Antimycotic	
Estrogen	Contraception, replacement therapy, prostatic cancer	Mild, sustained BP elevation, more common in premenopausal women, severe hypertension has been reported
Progesterone	Contraception, replacement therapy	
Androgens	Anabolic effect	Mild, dose-dependent sustained increase in systolic BP
Danazol (semisynthetic androgen)	(abuse in athletes)	Endometriosis, hereditary angioedema
Anesthetics and Narcotics		
Cocaine	Local anesthetics; street drug	Transient severe increase in BP, especially when used with propranolol
Ketamine hydrochloride	Anesthetic agent	Transient severe increase in BP
Fentanyl citrate	Narcotic analgesic and anesthetic agent	
Scopolamine	Preanesthetic medication, motion sickness	
Naloxone hydrochloride	Opioid overdose	Transient BP evaluation

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Table 4. Exogenous substance-induced hypertension (Part 2).

Ingredients	Common Use/Abuse	Notes
Drugs Affecting the Sympathetic Nervous System		
Phenylephrine hydrochloride	Upper respiratory decongestant; ophthalmic drops	Dose-dependent, sustained increase in BP
Dipivalyladrenaline hydrochloride	Ophthalmic drops	Severe HT has been reported; may precipitate myocardial events and therefore should be used with caution in patients with coronary disease
Epinephrine (with -blocker)	Local anesthetic, anaphylactic reaction, bronchodilatation, decongestant antihemorrhoidal treatment	
Phenylpropanolamine	Anorexic/decongestant	
Pseudoephedrine hydrochloride	Decongestant	
Tetrahydrozoline hydrochloride	Ophthalmic vasoconstrictor drops; ophthalmic vasoconstrictor and nasal decongestant drops	
Oxymetazoline hydrochloride	Decongestant drops	
Caffeine	Analgesia, vascular headache, beverages	Acute transient increases in BP
Metoclopramide	Antiemetic	Transient increase in BP in association with cancer chemotherapy
Alizapride	Antiemetic	
Prochlorperazine	Antiemetic	
Yohimbine hydrochloride	Impotence	Acute, dose-dependent increase in BP
Glucagon	Bowel spasm	Only in patients with pheochromocytoma
Physostigmine	Reverse anticholinergic syndrome	
Ritodrine hydrochloride	Inhibition of preterm labor	Hypertensive crisis has been reported
MAOIs	Antidepressive agents	Mainly with sympathomimetic amines and with certain foods containing tyramine
Tricyclic antidepressants	Antidepressive	More common in patients with panic disorders
Buspirone	Anxiolytic	Mild, dose-dependent increase in BP
Fluoxetine	Antidepressive	In combination with selegiline
Thioridazine hydrochloride	Psychotic and depressive disorder	Massive overdose may cause severe HT

Table 4. Exogenous substance-induced hypertension (Part 3).

Ingredients	Common Use/Abuse	Notes
Ions		
Sodium chloride	Food and Drugs	In salt-sensitive subjects
Lithium	Manic-depressive illness	Acute intoxication can cause severe HT
Calcium	Food and Drugs	
Lead	Industry	
Cadmium	Industry	
Mixed or Unknown Mechanism		
Cyclosporine	Immunosuppressive agent	Dose-dependent mild-to-moderate increase in BP; severe HT has been reported
Alkylating agents	Neoplastic disorder	
Recombinant human erythropoietin	Anemia or renal failure	Dose-related mild increase in BP; hypertensive crisis with encephalopathy has been reported
Bromocriptine mesylate	Suppression of lactation and prolactinoma	Severe HT with stroke has been reported after use for suppression of lactation
Disulfiram	Alcoholism	Slight increase in BP; severe HT may occur in alcoholic-induced liver disease
Alcohol	Various	Dose-dependent, sustained increase in BP
Nicotine	Cigarette smoking	Acute transient increase in BP
Nonsteroidal anti-inflammatory drugs including COX-2-specific inhibitors	Analgesic; anti-inflammatory agent	Mild, dose-dependent increase in BP
Long acting somatostatin	Gastrointestinal disorders	Severe hypertension in subjects with autonomic dysfunction

Adapted from [5].

acute elevation of intracranial pressure (ICP) leads to hypertension with bradycardia (Cushing response) and constitutes a preterminal event. Chronic elevation of ICP does not cause hypertension except when it is very severe.

Tumors of the posterior fossa seem to be more associated with hypertension than supratentorial neoplasms. This is probably related to their proximity to some stretch-sensitive receptor elements in the floor of the fourth ventricle. Rarely, brain lesions lead to a paroxysmal type of hypertension mimicking pheochromocytoma [20]. Neurogenic hypertension can be associated with paroxysmal headache and symptoms of excessive autonomic activity such as tachycardia, diaphoresis, anxiety, tremor, nausea, and vomiting. Flushing of the skin is common and, not unexpectedly, focal neurological signs are usually present. In 38% of the cases, catecholamines and their metabolites are elevated. Patients with features characteristic of pheochromocytoma who have neurological symptoms or signs or who have a negative workup and patients with increased urinary excretion of catecholamines or their metabolites but no evidence of pheochromocytoma on further studies should have an imaging study of the brain to rule out a brain tumor. MRI is preferable because of its superiority in detecting posterior fossa lesions. Similar presentation has been reported after cerebral infarction.

Patients with tranverse lesions of the cervical spinal cord above the origins of the thoracolumbar sympathetic neurons lose central control of their sympathetic outflow. Stimulation of nerves below the injury, as with bladder distension, can cause reflex sympathetic activity via the isolated spinal cord, resulting in hypertension, diaphoresis, flushing, and headache, a syndrome called autonomic hyperreflexia.

Excessive sympathetic nervous activity immediately following severe head injury can lead to a hyperdynamic state with hypertension. Treatment with a short-acting -blocker is preferable to vasodilators, which may further increase ICP.

Hypertension in Sleep Apnea Syndrome

It is estimated that sleep apnea affects 2 – 4% of middle-aged adults and is more prevalent in men. Most commonly it is secondary to upper airway obstruction by the surrounding structures during sleep. Systemic hypertension is seen in 60 – 80% of cases of sleep apnea syndrome. Snoring, sleep fragmentation, daytime somnolence, dysrhythmias, erythrocytosis, large neck size and obesity are other common manifestations. The relation between hypertension and sleep apnea is independent of obesity. It is thought that the repetitive hypoxemia and hypercapnia that result from the obstruction lead to increased sympathetic nervous system tone and neuroendocrine dysfunction with blood pressure elevation and increased risk for cardiovascular complications. Sleep studies should be done in hypertensive patients with a history of habitual snoring associated with daytime somnolence, observed apnea, or some of the other features discussed above. Weight loss, avoidance of CNS suppressant (including some antihypertensives), positive pressure breathing, oral devices, and various surgical interventions are used to treat this condition and usually result in improvement or even cure of the hypertension [21].

Stress and Hypertension

Stress, both physical and emotional, can lead to acute elevation of blood pressure that normalizes with the removal of the stressing situation. Erroneous diagnosis of chronic hypertension and committing the patient unnecessarily to lifelong antihypertensive therapy may result when the role of stressors is ignored. These patients' blood pressure is best treated by removing the cause and usually does not require antihypertensive therapy. Unfortunately, the use of sublingual, short-acting nifedipine to treat the blood pressure under these circumstances remains common despite documented cases of myocardial infarction and ischemic stroke resulting from hypotension and sympathetic overactivation caused by the rapid vasodilatation from this agent. It has been suggested that repeated episodes of stress-induced blood pressure elevation result in sustained hypertension, but this is yet to be proven.

Exogenous Substance-induced Hypertension

Many exogenous substances, including prescription and over-the-counter medications, foods, and substances used for recreational purposes, can raise the blood pressure or interfere with its treatment (Table 4) [2]. The COX-2-specific inhibitors in general have the same renal and hypertensive effects seen with nonsteroidal anti-inflammatory agents. These side effects are reported to be more severe with rofecoxib than celecoxib.

Caffeine and nicotine can transiently elevate the blood pressure, and measurements should not be done within 30 minutes of their use.

Drugs Affecting the Sympathetic Nervous System

Several drugs can directly or indirectly activate the sympathetic nervous system, leading to blood pressure elevation. These reactions are more likely to occur with larger doses of the drugs. The concomitant use of sympathomimetic agents and -blockers can lead to unopposed -adrenergic stimulation and sometimes a severe hypertensive reaction.

Cocaine blocks the reuptake of norepinephrine at sympathetic nerve terminals. Its abuse may cause severe hypertension, renal failure, and myocardial ischemia. During pregnancy it can lead to abruptio placentae and neonatal hypertension. It can also be confused with preeclampsia, because hypertension, headache, blurred vision, and abdominal pain are seen in both conditions. The combined use of cocaine and epinephrine paste in intranasal surgery has been reported to cause severe hypertension, myocardial ischemia, and arrhythmia, even in healthy subjects.

Alcohol

Alcohol consumption could be responsible for up to 11% of chronic hypertension cases seen in men in developed societies and an even higher proportion in some primitive so-

cieties. Women have lower prevalence of alcohol-induced hypertension because, on average, they drink less than men. The hypertensive response to chronic alcohol intake is seen once the consumption exceeds 1 – 2 drinks/day and is dose-related. Population studies suggest that for each standard drink per day, there is a 1 mmHg increase in systolic blood pressure. However, individual responses vary. Older age and obesity increase the hypertensive effect. The pressor response to alcohol develops within a few days of intake and recedes within 1 – 4 weeks of cessation.

The mechanisms involved in alcohol-induced hypertension are poorly understood. A direct vasoconstrictor effect and increased responsiveness of the vascular bed to pressors seem to play a role. Magnesium deficiency, common in alcoholics, can lead to increased intracellular calcium in vascular smooth muscle cells and sympathetic nerve terminals. In an animal model, magnesium supplementation prevented the development of alcohol-induced hypertension. Alcohol increases the secretion of corticotropin-releasing hormone (CRH), which stimulates ACTH production and sympathetic activity. Dexamethasone, which suppresses CRH release, has been shown to blunt the hypertensive reaction caused by acute alcohol administration [21].

Acute alcohol withdrawal and treatment with disulfiram cause hypertensive reactions, but abstinence from alcohol and even dose reduction lead to gradual improvement or normalization of blood pressure.

Psychiatric Medications

Monoamine oxidase inhibitors (MAOI) delay the metabolism of sympathomimetic amines and 5-hydroxytriptophan. They can cause a severe hypertensive reaction when patients taking them consume substances containing tyramine such as aged cheese and red wine, sympathomimetics, or serotonin reuptake inhibitors. Spontaneous hypertensive episodes have been reported. The reaction may mimic pheochromocytoma.

Rarely, tricyclic antidepressants have been reported to cause hypertension via an unclear mechanism. Methylphenidate (Ritalin), used to treat children with attention deficit disorder, has been reported to raise diastolic blood pressure in some children taking it. Buspirone, an anxiolytic, can cause hypertension thought to be the result of $_2$-antagonism caused by one of its metabolites.

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Special Problems in Managing Arterial Hypertension

Friedrich C. Luft

The value of lowering blood pressure to decrease the likelihood of stroke, myocardial infarction, vascular disease, and the progression of renal disease is undisputed. General approaches to hypertensive patients and specific concerns regarding hypertension related to renal disease, renovascular disease, transplantation, pregnancy, and hypertension in childhood and adolescence are presented as separate chapters. This chapter discusses special problems in certain subsets of hypertensive patients not considered elsewhere in this textboook.

Hypertension in the Elderly

Older patients' risks for stroke, myocardial infarction, or renal failure are much greater than that of younger patients. Six excellent recent studies document the decreased stroke risk, decreased myocardial infarction risk, and even increased life expectancy in elderly patients treated for hypertension [1]. Isolated systolic hypertension, which is much more common in the elderly, should also be treated. All 6 studies relied on thiazide therapy, while beta blockers were first-or second-line treatment in 4 studies. The incidence of fatal stroke was reduced by 33%, fatal coronary events by 26%, and cardiovascular mortality by 22%. However, there are special problems in the elderly.

Cardiac function is often decreased in the elderly. The aged ventricle is less able to relax and diastolic heart failure is more common. The increase in left ventricular mass in the elderly has similar negative prognostic implications as for younger hypertensive patients. Data from the Framingham study indicated that increased left ventricular mass-to-height ratios in the elderly were associated with an increased risk for stroke [2]. Renal function is decreased in the elderly, which may contribute in part to salt-sensitivity, and the baroreceptor reflex is impaired. The latter results in inordinate swings in blood pressure and postural hypotension (so called pseudo-pheochromocytoma). All antihypertensive drugs with rapid onset and brisk action should be avoided. An interesting hypothesis has been proposed suggesting that the rigidity of the carotid arteries causes a relative lack of neuronal input to the medulla during the usual blood pressure variations. This lack of input fosters sensitization of the reflex arc so that overreaction of the short-term blood pressure control system occurs, thereby leading to instability in both directions. Alpha blockers and nonselective beta blockers may cause problems in this regard. Centrally-acting drugs, especially moxonidine, may be particularly helpful by decreasing sympathetic tone and increasing baroreceptor sensitivity.

Despite tremendous recent progress, the treatment of hypertension in the elderly is not ideal. In the Systolic Hypertension in the Elderly Program, one-third of patients did not

reach goal blood pressure, 13% stopped treatment because of side effects, and 21% required a third drug to lower their systolic blood pressures [3]. Newer agents, such as endopeptidase inhibitors, renin inhibitors, angiotensin receptor blockers, and T-type calcium channel blockers may offer additional options; however, these drugs await further testing in elderly patients. Finally, ancillary measures of risk reduction must be considered. Lipid-lowering drugs decrease risk in the elderly, and secondary prevention strategies should be considered. In women of advanced age, hormone (estrogen) preparations may improve the quality of life and prolong life, even if administered long after menopause [4].

Preparation for Surgery

Not infrequently physicians are faced with the dilemma of patients who urgently need to be operated upon but whose blood pressure is not adequately controlled. In patients with a diastolic pressure < 110 mmHg, surgery is generally safe, provided that adequate anesthesia skills are available and that medications are continued until immediately before the operation. If the diastolic blood pressure exceeds 110 mmHg, the operation should be delayed if possible. There is good reason to continue beta blockers throughout surgery and to begin beta blockers in patients not receiving them. In a recent prospective clinical trial, middle-aged but not necessarily hypertensive patients were randomized to receive intravenous (IV) atenolol or placebo immediately before induction of anesthesia [5]. Atenolol 50 mg twice daily or placebo was continued until the patient was discharged. Patients given atenolol had a lower cardiovascular mortality or morbidity. Surprisingly, although the beta blocker treatment was given only in the perioperative period, the protective effect was still detectable 2 years later. Thus, beta blockers are indicated for middle-aged patients before routine operations if they have cardiovascular risks, irrespective of their blood pressure values.

In addition to beta blockers, clonidine provides a convenient option, particularly since it can be administered via a patch. Thus, in patients not able to ingest medication, effective treatment is nonetheless provided. Antihypertensive drugs that should not be given to patients preoperatively include guanethidine, guanadrel, guanabenz, and monoamine oxidase inhibitors. Such drugs may interfere with or potentiate the effect of norepinephrine. In patients receiving long-term diuretic treatment, physicians should consider the possibility of total body potassium depletion and consider strategies for its replacement.

Occasionally, severe perioperative hypertension occurs, particularly after cardiovascular surgery. A central mechanism with sympathetic activation may be responsible. Ketanserin, a selective S_2-serotonin receptor blocker with $alpha_1$-adrenergic blocking effects, may be a suitable antihypertensive medication after coronary artery surgery and lacks side effects seen with other vasodilators [6]. In a randomized trial, a calcium antagonist isradipine and sodium nitroprusside were compared in the management of hypertension in the early period following coronary artery bypass grafting (CABG) [7]. The authors concluded that isradipine was effective and well tolerated in the treatment of hypertension following CABG. The drug has a hemodynamic profile that may be more favorable than that seen after treatment with sodium nitroprusside. Postoperatively, antihypertensive medications should be reintroduced as soon as possible. In persons not able to take oral medi-

cations, parenteral labetalol, other beta blockers, parenteral ACE inhibitors, or the clonidine patch provide convenient alternatives.

Coarctation of the Aorta

Coarctation of the aorta can result in severe upper body hypertension. A 20 mm Hg difference in upper and lower extremity blood pressure or greater, a delay in the femoral pulse, and a midscapular murmur are generally found. Surgical correction should almost always be considered. In fact, surgery for coarctation of the aorta gives very good results modulated by the risk of recurrence, especially when performed early (before 6 months of age). Medical-surgical management of this congenital vascular disease begins at birth. Surgery should be performed before the end of the second year of life, allowing for nearly normal life, both at home and at school. Coarctation is generally considered a disease of infancy and childhood; however, occasionally it is also detected in the elderly. A 72-year-old man with long-standing moderate hypertension due to an aortic coarctation was recently reported [8]. He presented with a myocardial infarction. In view of his advanced age, the aortic coarctation was treated conservatively.

Preoperative and postoperative blood pressure management is best achieved with sympatholytic agents. Beta blockers are usually most helpful in this regard. Associated abnormalities may include a bicuspid aortic valve, ventricular septal defect, or Turner syndrome. The latter should be ruled out in all female patients. Coarctation is usually congenital; however, physicians should consider the possibility of Takayasu arteritis, which may involve the aorta as well as other great vessels. Some coarctation patients have been treated successfully with balloon dilatation. Stent implantation has recently provided a promising therapeutic alternative. In a recently reported series [9], all six patients were hypertensive (systolic blood pressure > 140 mmHg) before stent implantation. At mean follow-up of 8 months, 3 patients were normotensive. There was no recurrence of coarctation, aortic dissection, or aneurysm formation in the patients in whom stent implantation was successful. These findings indicate that balloon-expandable stent implantation for coarctation of the aorta in selected patients is a safe and effective alternative approach for relieving the obstruction with a low complication rate and no recoarctation at short-term follow-up. Long-term follow-up will be necessary to adequately evaluate this procedure.

Cushing Syndrome

Hypertension generally accompanies Cushing syndrome. The causes of Cushing syndrome are excess adrenocortico-tropic hormone (ACTH), excess ACTH-independent cortisol production in the adrenal gland, and iatrogenic or factitious ingestion of excess corticoid. Pituitary overproduction of ACTH (Cushing disease) accounts for the majority of noniatrogenic-induced Cushing syndrome. Ectopic production of ACTH by malignant tumors, most commonly lung, thymus, pancreas, and kidney, usually result in acute hyperadrenocorticism, dominated by mineralocorticoid effects. Hypokalemic alkalosis, weakness, proximal muscle wasting, and weight loss are outstanding elements; the Cushingoid habitus is less common. High alcohol intake and obesity, both of which are associated with hypertension, are the most

common differential diagnoses. Not all hypertensive patients need be tested for Cushing syndrome; however, the prudent clinician will keep the diagnosis in mind. The easiest screening tests are morning and evening cortisol levels to test for diurnal variation, followed by 1 mg dexamethasone taken at midnight, followed by another morning cortisol level. The 24-hour urinary free cortisol level is an alternative. Treatment is directed at the primary disease. Spironolactone may be used to counter the mineralocorticoid effects of hyperadrenocorticism.

Recently, the blood pressure-lowering results of operative treatment in 54 patients with Cushing syndrome was reported [10]. All patients were hypertensive preoperatively. Postoperatively, 39 had normal cortisol values and normal blood pressures. The duration of hypertension was predictive of success. Long-lasting exposure to cortisol appeared to be a determinant of persistent hypertension following surgery.

Oral Contraceptives

Estrogen-containing oral contraceptives may elevate systolic and diastolic blood pressure slightly in women taking them for prolonged periods of time. Oral contraceptives induce hypertension in approximately 5% of users of high-dose pills that contain ≥ 50 μg estrogen and 1 – 4 mg progestin; and small increases in blood pressure have been reported even among users of modern low-dose formulations. However, neither the responsible hormone in the oral contraceptive nor particular subgroups of women who might be susceptible to the hypertensive effect of oral contraceptives have been identified. In a recent prospective cohort study, 68,297 female nurses aged 25 – 42 years and free of diagnosed hypertension, diabetes, coronary heart disease, stroke, and cancer at baseline were followed for 4 years [11]. There were no important modifying effects of age, family history of hypertension, ethnicity, or body mass index in these women. The authors found that current users of oral contraceptives had a significant, moderately increased risk of hypertension. However, among this group, only 41.5 cases per 10,000 person-years could be attributed to oral contraceptive use. Risk decreased quickly with cessation of oral contraceptives, and past users appeared to have only a slightly increased risk. Thus, the risk of hypertension with current oral contraceptives is small.

Hypertension remains in about one-half of patients when oral contraceptives are discontinued. Because this phenomenon is more common in older women, it is not known for certain whether or not these women have essential hypertension that otherwise would not have been uncovered. Information about a family history of high blood pressure, the presence of renal disease, and presence of hypertension during pregnancy should be sought. Women with these features should be advised not to take oral contraceptives. An increase in blood pressure > 10 – 15 mmHg should prompt their discontinuation.

Pheochromocytoma

The diagnosis of pheochromocytoma has been simplified through improvements in biochemical assays for catecholamines and their metabolites, as well as in imaging techniques such as meta-iodobenzylguanidine scans and magnetic resonance imaging (MRI) [12]. Alpha blockade should be started initially with

phenoxybenzamine at a dosage of 10 mg twice daily. The dose is increased until adequate blood pressure control is achieved. Thereafter, the beta receptors should also be blocked. Propranolol 10 mg, 4 times daily may be begun and a longer-acting formulation substituted when the desired effect is achieved. The rationale for this approach is to avoid interfering with any beta-mediated vasodilatation in such patients before alpha blockade is achieved. Labetalol has also been found useful in patients with pheochromocytoma and provides an alternative drug treatment. Novel treatment attempts with octreotide to block catecholamine release have proved disappointing [13].

Surgery should be undertaken when blood pressure control is complete. Careful intraoperative monitoring is mandatory. Manipulation of the tumor may cause severe hypertension and tachyarrhythmias, even in well-prepared patients. The anesthesiologist must be prepared to treat such fluctuations in blood pressure with phentolamine and propranolol. With drug treatment or with tumor removal, considerable volume expansion with normal saline or, rarely, other volume expanders may be necessary to combat marked decreases in blood pressure or even shock. In terms of the operative methods, the transabdominal method is associated with greater morbidity than the retroperitoneal approach. Recently, laparoscopic adrenalectomy has been successfully introduced in the operative treatment of pheochromocytoma [14]. Malignant pheochromocytomas do occur. Cyclophosphamide, vincristine, and dacarbazine have been employed. Therapeutic doses of ^{131}I meta-iodobenzylguanidine have also been employed with good results [15].

Finally, the possibility of a genetic cause, such as of multiple endocrine neoplasia (MEN) type II, von Hippel-Lindau syndrome, and neurofibromatosis should always be considered [16]. Each of these conditions necessitates a long-term strategy for the entire family. Each can be diagnosed with molecular genetic techniques.

Primary Aldosteronism

Primary aldosteronism results from a benign adrenal adenoma (Conn syndrome) or bilateral adrenal hyperplasia (idiopathic aldosteronism). The former is more common than the latter. Distinguishing between these 2 forms of aldosteronism is important, because only adenomas should be operatively removed. Bilateral adrenalectomy in adrenal hyperplasia has reversed hypertension in only about one-third of patients. When considering the diagnosis of primary aldosteronism, physicians should also consider the possibility of glucocorticoid-remediable aldosteronism. A detailed family history should be obtained in every patient, and if an adenoma cannot be readily identified, special tests for glucocorticoid remediable aldosteronism should be done [17]. With upright posture, serum aldosterone values usually decrease in patients with adrenal adenomas and remain constant in patients with adrenal hyperplasia [18]. Computed tomography (CT) and MRI will usually visualize adenomas, although their small size may make adrenal vein blood sampling necessary. In patients with adrenal hyperplasia, blood pressure should be controlled with spironolactone. Doses up to 200 mg daily may be necessary. If spironolactone is not tolerated, amiloride 10 – 30 mg daily may be substituted. Excessive licorice ingestion (> 0.45 kg/week) should be considered in the differential diagnosis of adrenal hyperplasia. Glycyrrhizic acid in licorice and in flavored chewing tobacco interferes with the enzyme

11-β OH steroid dehydrogenase, which normally metabolizes cortisol to cortisone in distal renal tubular cells. Under such circumstances, cortisol may occupy the mineralocorticoid receptor, resulting in volume expansion, hypokalemia, and hypertension.

Primary aldosteronism is generally treated operatively. Recently, Celen et al. [19] reported on 42 patients undergoing surgical treatment. Twenty-five patients became normotensive without medications. Predictors of a good outcome were younger age, duration of hypertension < 5 years, and preoperative response to spironolactone. The presence of micronodular hyperplasia was an inverse predictor. CT was as helpful in making the diagnosis as iodocholesterol scintigraphy (75%) but was less accurate than renal vein sampling (95%).

Hypertensive Urgencies and Emergencies

The term "hypertensive crisis" is commonly used by physicians to denote patients with high blood pressure values who are hospitalized for that reason. It is frequently difficult to discern whether it is the patient or the physician having the crisis. The term should not be used loosely. However, there are instances in which blood pressure should be lowered rapidly or even acutely. Exacting definitions are important to avoid inappropriate therapeutic decisions [20]. Accelerated and malignant hypertension is believed to be on the decline; however, that impression may be erroneous. In a recent report, Lip et al. observed that in a multiracial English population, malignant hypertension had not declined over a 24-year survey [21].

Accelerated Hypertension and Hypertensive Urgencies

In accelerated hypertension, the development of end-organ damage is telescoped into a short period of time instead of over many years. Less than 1% of hypertensive patients develop accelerated hypertension, usually when the hypertension is poorly controlled or not treated. Accelerated hypertension is more frequent when the hypertension is secondary, for example as in patients with renovascular hypertension or pheochromocytoma, patients with glomerulonephritis, generalized vasculitis, or preeclampsia. The renin-angiotensin system frequently plays an important role in the pathogenesis of accelerated hypertension.

End-organ damage may be discerned in patients with accelerated hypertension. The funduscopic examination reveals not only arteriolar narrowing and arteriolar-venous crossing abnormalities, but also hemorrhages and exudates. The heart is enlarged and a fourth heart sound is generally audible. Signs of congestive heart failure may be present. Urinalysis reveals the presence of proteinuria and casts. Serum creatinine and blood urea nitrogen (BUN) may be elevated. Diastolic blood pressure is frequently > 130 mm Hg. Patients with accelerated hypertension are generally best admitted to the hospital and treated intensively with medications. An appropriate diagnostic work-up (renal angiography, for example) should be initiated. These patients present a hypertensive *urgency*. They should have their blood pressure lowered with oral medication over a period of several days. They do not require a blood pressure reduction in minutes to hours.

Hypertensive Emergencies (Hypertensive Crisis)

Patients who have severe hypertension and concomitantly have a dissecting aortic aneurysm, a stroke in evolution, an acute myocardial infarction (MI), acute pulmonary edema, eclampsia, acute renal failure (ARF), uncontrolled pheochromocytoma, or encephalopathy are true hypertensive emergencies. Each is discussed separately below. Such patients require continuous (intra-arterial or oscillometric) blood pressure monitoring, and they should be admitted to an intensive care unit. The diagnosis is seldom subtle. Dissecting aortic aneurysms can be readily diagnosed with transesophageal echocardiograhy, CT, or MRI. In patients with stroke, ischemic stroke must be differentiated from intracranial hemorrhage and CT is indicated. The diagnosis of hypertensive encephalopathy requires a careful history and assessment of mental status (mini-mental status test). Papilledema is frequently but not invariably present and may not be a reliable finding; however, hemorrhages and exudates are generally found on funduscopic examination. In the intensive care unit, continuous arterial, central venous, intracranial, and pulmonary capillary wedge pressures, as well as urinary output should be monitored as called for by the clinical situation.

Tailored treatment is necessary [22]. Patients with neurological defects and increased intracranial pressure frequently develop marked increases in blood pressure. Their primary problem should be addressed, not merely their arterial pressure. Patients with acute MI and/or pulmonary edema should have this primary problem addressed. Patients with dissecting aortic aneurysms require modification of their pulse pressure curve and very specific pharmacologic therapy. Patients with eclampsia or pheochromocytoma also require very specific care. A schema for handling hypertensive urgencies and emergencies is given in Figure 1.

Drug Therapy for Hypertensive Urgencies and Emergencies

The practice of cracking open a nifedipine capsule and having the patients chew on it to lower blood pressure acutely should be abandoned [23]. First, several pharmacokinetic studies have demonstrated that nifedipine is not absorbed by the oral mucosa or by the esophagus. Absorption via the oral route occurs in the upper small intestine. Second, in the United States, short-acting nifedipine is not approved for lowering blood pressure. Recently, evidence was reviewed indicating that the use of nifedipine in this fashion is accompanied by frequent complications. Most were due to too rapid reductions in blood pressure with subsequent cerebral, cardiac, or renal ischemia. Therefore, stroke, myocardial infarction, or, rarely, renal failure may ensue. Hypertensive *urgencies* should be aggressively treated with oral medications to lower blood pressure within hours to days. Hypertensive *emergencies* should be treated with appropriate monitoring in the intensive care unit, and parenteral agents may be necessary.

Sodium Nitroprusside and Parenteral Nitroglycerine

These potent smooth-muscle relaxants are particularly useful in patients with ischemic heart disease because they do not impair myocardial blood flow. Nitroglycerine is particularly helpful in patients with heart failure because its effect is largely exercised in the

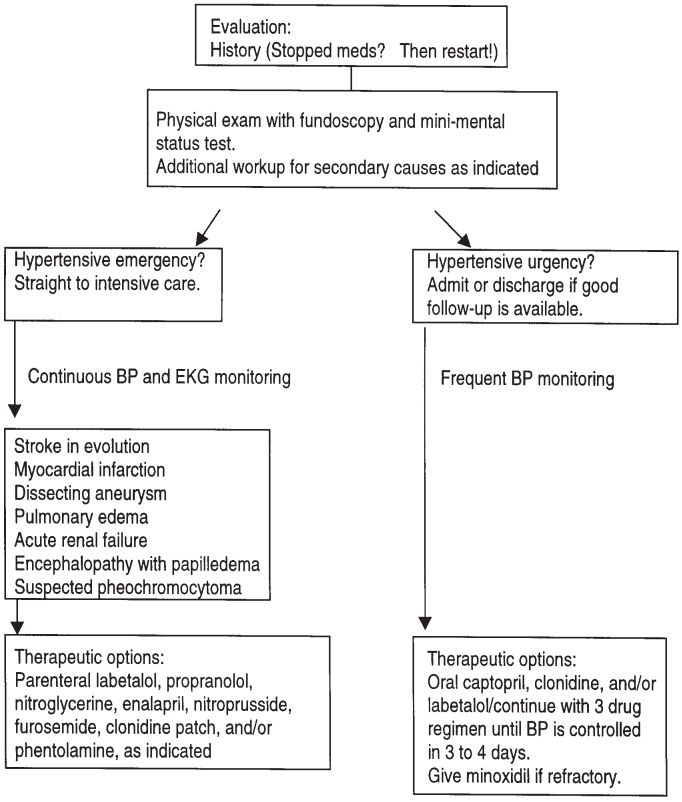

Figure 1. Approach to accelerated or emergent hypertension (diastolic BP > 120 mm Hg); evaluate and treat immediately.

venous circulation, resulting in a reduction in preload. Sodium nitroprusside is metabolized to cyanide and thiocyanate. Prolonged use may lead to toxicity manifested by lactic acidosis, methemoglobinemia, muscle weakness, hyperreflexia, confusion, delirium, and coma. Blood thiocyanate levels can be monitored; however, keeping the therapy brief is an appropriate strategy. Nitroglycerine does not exhibit these disadvantages.

Trimethaphan

Trimethaphan is a rapidly acting ganglionic blocker. The drug induces tachyphylaxis. The head of the patient's bed should be elevated for maximal effects. Trimethaphan is an alternative choice in the treatment of dissecting aortic aneurysms. Otherwise, the drug is primarily of historic interest.

Nifedipine

Nifedipine has been recommended by several expert groups for the treatment of hypertensive emergencies and urgencies. The drug is given orally and should not be chewed or given sublingually. A 10 – 20 mg dose will lower blood pressure within minutes. Because nifedipine is a vasodilator, overshoot hypotension, particularly in hypovolemic patients, may occur. Nifedipine also increases heart rate and circulating catecholamines. Coronary insufficiency in patients with coronary

arterial stenosis has been reported via a "steal" phenomenon related to the distribution of coronary blood flow elsewhere.

Diazoxide

This potent vasodilator is structurally related to the thiazide diuretics. Intravenous infusion is effective within 20 minutes. Side effects include hyperglycemia and fluid retention. The following can be avoided by simultaneously administering furosemide. Reflex tachycardia and an increase in cardiac output occur and angina pectoris and myocardial infarction can be precipitated. The drug is contraindicated in patients with acute MI or with dissecting aortic aneurysms. Today the compound is primarily of historical interest.

Hydralazine

Parenteral hydralazine is still commonly used to treat hypertensive patients with preeclampsia or eclampsia. The drug is effective within 20 minutes. Treatment should begin with a low dose (10 mg) to avoid overshoot hypotension. Hydralazine should not be given to patients with acute myocardial infarction or coronary syndromes. Beta blockade is advisable to avoid reflex tachycardia.

Labetalol and Other Beta Blockers

Intravenous labetalol is useful for rapid reduction of blood pressure. The drug can be administered parenterally in 20 – 80 mg doses at 10-minute intervals and is suitable for patients with coronary artery disease, impaired hemodynamics, or dissecting aortic aneurysms. The drug is also helpful if pheochromocytoma is suspected and may be given to patients with eclampsia. The beta blocking effects should engender caution in patients with bronchospasm, atrioventricular conduction defects, and bradycardia. If rapid sole beta blockade is desired, for instance, in patients with aortic dissection, propranolol or esmolol, a very rapid-acting beta blocker, can be given parenterally. The same precautions should be exercised.

ACE Inhibitors

A parenteral formulation of enalapril is available. Captopril 12.5 – 50 mg may be given orally to rapidly lower blood pressure within 1 – 2 hours. The dose can be repeated every 4 hours until the desired control is achieved. ACE inhibitors should not be given to pregnant women.

Clonidine

Clonidine is effective in a 2- to 5-hour period when given orally. An initial dose of 0.1 – 0.2 mg should be given orally and may be followed by 0.1 mg/hour to a total dose of 0.7 mg until the desired effect is achieved. Clonidine has proved especially valuable in cocaine and methamphetamine abusers, as well as patients experiencing withdrawal states. The patch formulation is convenient.

Urapidil

Urapidil provides peripheral alpha receptor blockade and also has a central mode of action. A parenteral formulation is available.

Specific Hypertension-related Urgencies and Emergencies

Acute Pulmonary Edema

Treatment should be directed at the congestive heart failure (CHF). IV nitroglycerine and a loop diuretic are indicated. An ACE inhibitor can be considered acutely, and parenteral formulations are available. Finally, albeit old-fashioned, judicious use of IV morphine is often extremely helpful in such patients.

Acute Myocardial Infarction (MI)

There is no evidence that lowering arterial pressure influences infarct size. Nitroglycerine is indicated. Beta blockers are of proven value in acute MI, and labetalol or other beta blocker should be given. Acute parenteral treatment with an ACE inhibitor is probably not indicated according to the results of the *Consensus II* study. However, judicious orally administered ACE inhibitor therapy after the second day is appropriate.

Aortic Dissection

Most patients with aortic dissection have a history of hypertension. Physicians should be aware of the genetic nature of this malady. Patients with mutations in the fibrillin gene may exhibit stigmata of Marfan syndrome but may also be completely normal in appearance. Patients with dissections involving the aortic root or the carotids and patients with aortic insufficiency should be considered for acute intervention. Dissections beginning distal to the left subclavian artery are best treated medically. The treatment is aimed at containing the progression of the hematoma by reducing blood pressure and by lessening the velocity of myocardial contraction (*dp/dt*). Propranolol 0.5 mg should be given as a test dose intravenously, followed by repeated 1 mg doses at 5-minute intervals. Oral therapy should be begun as soon as possible. Concomitantly, nitroglycerine or nitroprusside should be given by continuous infusion titrated to the arterial blood pressure. Oral therapy with a beta blocker, ACE inhibitor, and diuretics should be achieved after the patient has been stabilized.

Pheochromocytoma Crisis

This condition is best treated acutely with alpha1-receptor blockade. Phentolamine is given at a dose of 2 – 5 mg intravenously every 5 minutes until the blood pressure is controlled. Beta blockade should ideally be delayed initially so as not to interfere with beta-mediated vasodilatation in the setting of alpha-adrenergic vasoconstriction. Oral therapy with phenoxybenzamine and a beta blocker, or alternatively with labetalol, can be commenced once parenteral control is achieved.

Preeclampsia and Eclampsia (see also separate chapter I-9)

Prompt delivery should be considered if possible [24]. The rapid extreme correction of hypertension in patients with eclampsia can further compromise placental blood flow, thereby aggravating the condition. IV hydralazine has been advocated at an initial 5 mg dose, followed by 5 – 10 mg every 20 minutes.

Labetalol or beta blockade should be considered. A number of drugs are contraindicated during pregnancy, including sodium nitroprusside, which may cause fetal cyanide poisoning; ganglionic blocking drugs, which may cause meconium ileus; and ACE inhibitors, which may cause fetal death. Magnesium sulfate 2 – 4 g over 15 minutes IV followed by a continuous infusion of 1 – 2 g/hour is still the preferred treatment for eclampsia according to several recent clinical trials [25].

Cerebrovascular Syndromes

Rapid diagnosis is necessary and neurosurgical consultation should be obtained if cerebral hemorrhage is found. Hypertension secondary to expanding intracerebral masses does not respond well to drugs. Hematomas in the putamen, subcortical white matter, and cerebellum are generally operated upon, while those in the thalamus and pons are usually managed conservatively. Subarachnoid hemorrhage is usually operated upon immediately or managed with sedation, bed rest, and gentle reduction of blood pressure with oral agents. Nimodipine has been advocated for this purpose. Blood pressure should be lowered very carefully in patients with thrombotic or embolic stroke. According to a European conference of neurologists, blood pressure should be lowered only if the pressure exceeds 220/120 mm Hg. Reductions should be made very cautiously to no lower than 160/100 mm Hg. Autoregulation of cerebral blood flow is shifted markedly to the right in accelerated hypertension, and a brisk reduction in blood pressure may result in ischemia. Rapid reduction of blood pressure can aggravate the neurological defect, particularly if a major blood flow obstruction exists. Careful administration of oral agents is the rule. If a vasodilator is given, concomitant beta blocker therapy is advisable. Finally, the head of the bed should be elevated for patients with cerebrovascular syndromes.

The Heart in Hypertension

Epidemiology

The myocardium undergoes structural changes in response to hypertension, and these changes are collectively termed hypertensive heart disease. The left ventricular hypertrophy (LVH) associated with hypertension is unique in several respects and is fundamentally different from the LVH following aerobic exercise, high output states, or valvular heart disease. Traditional thinking considered LVH to be a positive adaptive mechanism in response to an increased hemodynamic load. However, epidemiological evidence from electrocardiographic (ECG) and echocardiographic studies strongly suggests that this view is incorrect. Hypertension-associated LVH is an independent risk factor for cardiovascular morbidity and mortality, including MI, CHF, and sudden cardiac death [26]. For instance, electrocardiographically-determined LVH conferred a 3-fold elevated risk of subsequent coronary heart disease, even after correction for the blood pressure level. In addition to myocardial infarction, LVH was a strong predictor of congestive heart failure as well as sudden death in hypertensive patients. Thus, LVH may actually indicate the presence of a second disease, namely myocardial ischemia. Studies of the coronary blood flow reserve demonstrate marked impairment in patients with hypertensive heart disease, which may be ameliorated by drug treatment.

Diagnosis

Echocardiography is the best method to diagnose hypertensive heart disease [27]. The echocardiographically determined LV mass correlates closely with the anatomically determined LV weight. In contrast, casual blood pressure measurements correlate poorly with either echocardiographically or anatomically determined LV mass. Ambulatory 24-hour measurements are better in this regard and account for about 25% of the variance in LV mass ($r = 0.25$). Age and gender have independent effects. Patients with echocardiographically-determined LVH had a 5-fold higher cardiovascular event rate compared to those without LVH, despite similar blood pressure values. Longitudinal studies corroborated and underscored earlier cross-sectional observations. Longitudinal studies also suggested that assessment of the blood pressure load with 24-hour ambulatory measurements is of value in selecting individuals with LVH. Thus, the independence of LVH from blood pressure may be more apparent than real.

Echocardiographically-determined LV mass varies, and the technique is subject to errors. Meticulous attention to technique in performance and standardization of echocardiography is necessary. In a 2-dimensional, targeted, M-mode Doppler echocardiographic study in 96 patients with essential hypertension who were studied twice, the interclass coefficient of correlation was 0.86 for LV mass and 0.82 for LV mass index. However, the 95% confidence interval was considerable. If different individuals using different machines perform the echocardiography, even more variability can be expected. Nevertheless, misclassification is unlikely in persons who are clearly in the normal range or in those with obviously elevated LV mass.

Which hypertensive patients should undergo echocardiography? According to current guidelines by the Canadian Hypertension Society, "There is insufficient evidence at present to recommend echocardiography for routine clinical use in evaluating mild hypertension or in making decisions about the initiation of treatment for mild hypertension" [28]. For similar reasons, follow-up echocardiography to assess effectiveness of antihypertensive (drug) therapy is currently of limited value. Echocardiography can be considered for patients who have moderate to severe hypertension, particularly if clinical findings and baseline tests alert to the presence of cardiac involvement or heart disease.

Pathogenesis

The molecular mechanisms of myocardial hypertrophy are actively being studied. External mechanical stress on cardiac myocytes leads to activation of phospholipase C, which in turn leads to the production of inositol phosphate by degradation of membrane phospholipids. Inositol phosphate production leads to protein kinase C activation. Activated protein kinase C serves to activate the mitogen-activated protein kinase (MAP-kinase) pathway. Accordingly, Raf-1 kinase, MAP-kinase, and S6 kinase are all activated, thus activating the transcription factor activator protein-1 (AP-1) and thereby increasing the expression of immediate early genes (particularly *c-fos*) in the cell nucleus [29]. This process leads to increased transcription in the nucleus as well as increased biosynthesis of myocardial proteins (translation) in ribosomes. The increased production of proteins is necessary for cell hypertrophy and cardiac hypertrophy.

A major stimulus for LVH is the vascular load on the heart that results from peripheral vasoconstriction. The renin-angiotensin system appears pivotal. Ang II is a major factor

in vascular overload and may be a direct stimulus for hypertrophy. Aldosterone may be important in its own right, particularly in promoting fibroblast proliferation in the myocardium. Thyroid hormone also stimulates hypertrophy, but clinically is of secondary importance. Increased adrenergic activity has been implicated in promoting LVH. Environmental factors may be important in the development of LVH. For instance a high salt intake, particularly in persons unable to suppress their Ang II values in the face of a high salt intake, has been implicated in LVH development. Finally, genetic predisposition has been implicated. Strong evidence from twin studies demonstrates the effect of genetic variance on heart size. Furthermore, these same studies suggest that the insertion/deletion polymorphism in the ACE gene (the D allele is associated with higher ACE levels) specifically influences left ventricular size [30].

LVH and Heart Failure

Heart failure in hypertension may be primarily *diastolic*. In several studies, hypertensive patients hospitalized for CHF commonly (40%) had systolic function that was preserved or normal. In normal subjects, diastolic LV volume increases dramatically when the pressure is still falling, creating a suction of blood across the mitral valve from the atrium to the ventricle. This mechanism permits an increase in end-diastolic volume and stroke volume during exercise, despite the shorter diastolic filling time that occurs with tachycardia. In hypertension, LV filing pressure is shifted upward compared with normal diastolic filling. Thus, for any given LV volume there is a higher LV filling pressure. Furthermore, in hypertensive LVH there is an impairment of Ca^{2+}-dependent relaxation in diastole. This feature also contributes directly to abnormal filling, particularly during exercise. In untreated hypertensive patients, pulmonary capillary wedge pressure increases dramatically with low levels of workload despite preserved systolic function. This response can be favorably influenced by treatment.

Late diastolic filling is determined by atrial contraction and LV stiffness. The preservation of atrial contraction is important to provide normal loading conditions for the ventricle, and considerable left atrial hypertrophy is required to provide an effective atrial systolic contraction when the ventricle is stiff. Under these conditions a fourth (atrial gallop rhythm) heart sound is audible. Clinicians should always look for the S4 gallop when examining hypertensive patients. The development of atrial fibrillation indicates a greater propensity for clinical heart failure.

CHF featuring systolic dysfunction obviously also occurs in hypertensive heart disease. Autopsy studies have shown that hypertrophied cardiac myocytes undergo degenerative changes accompanied by increased collagen deposition and fibrosis. In hypertension, these cellular changes reflect the outcome of chronic adaptive responses, so that the absolute level of blood pressure may no longer correlate well with the extent of LVH. Not properly appreciated is the fact that coronary flow and resistance are abnormal in hypertension. Compared to normal subjects, flow is reduced and resistance is increased. The decrease in coronary “reserve” (defined as the increase in coronary flow observed with vasodilator treatment measured during cardiac catheterization) is most pronounced in patients with the “strain” pattern on their ECG. Thus, myocardial ischemia and decreased coronary reserve play an important role in systolic ventricular dysfunction. Moreover, the angina pectoris often seen clinically in hypertensive patients with patent main coronary arteries may be related to this phenomenon.

The progression of hypertensive heart disease, from remodeling to diastolic or systolic heart failure or both, typically requires decades. Treatment of hypertension in the elderly provides some insight into the therapeutic impact on this process. The trials of hypertensive treatment in the elderly showed that even with simple protocols, there was a significant reduction of morbidity and mortality, particularly in terms of CHF. Of the morbid events that were followed in these trials, the reduction in the incidence of heart failure was associated most strongly with the blood pressure reduction. This finding demonstrates a favorable treatment effect on both systolic and diastolic function. Not all hypertensive heart disease need be secondary to hypertension. Coexistent coronary artery disease commonly plays a role. Idiopathic cardiomyopathy may occur in the setting of antecedent hypertension. Hypertension and heart failure may coexist and contribute to one another, such as is commonly seen in chronic dialysis patients.

Treatment

The key to treating hypertensive cardiovascular disease is in getting the blood pressure down. Nevertheless, specific drug treatment may be helpful. There are no long-term comparative trials of LVH regression. In the TOMHS study, in which patients were followed echocardiographically over 4 years, all drugs were helpful, including the thiazide diuretics [31]. Because the renin-angiotensin system plays an important role in LVH, the use of ACE inhibitors has been favored, and indeed meta-analyses support their use. An ACE inhibitor should be included in any regimen for CHF. In diastolic dysfunction, an increase in relaxation time should be achieved, and beta blocker therapy is helpful in this regard. Physicians must remember to begin beta blocker therapy slowly in patients with heart failure of any cause. Several large studies showing a beneficial effect of carvedilol have recently been published, and trials with other beta blockers are underway. Long-acting dihydropyridine calcium channel blockers and verapamil appear to improve diastolic filling. A careful combination of long-acting dihydropyridine-beta blocker regimen could be considered. Diuretic therapy in patients with diastolic dysfunction may be counterproductive because ventricular filling could be curtailed further. Hypertensive heart disease associated with systolic heart failure requires diuretic and ACE inhibitor treatment. Digitalis may be helpful under these circumstances. In terms of lowering blood pressure in the face of significant LV systolic failure, the goal should be in the 120 mm Hg range rather than the traditional endpoints.

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Hypertension in Children and Adolescents

Karl Schärer

The interest in arterial hypertension on the part of pediatricians has traditionally been rather limited, one reason being that involvement of target organs was recognized only recently in children and adolescents. This situation has changed over the last 10 – 20 years. The incorporation of blood pressure measurements in routine pediatric examination and the expansion of accurate blood pressure monitoring equipment have facilitated the detection and evaluation of childhood hypertension. The concept that primary (essential) hypertension in adults has its root in childhood has enforced the idea of early prevention by regular blood pressure screening [35]. In addition, the increasing survival of pediatric patients with chronic disorders associated with hypertension such as aortic coarctation or end-stage renal disease (ESRD) has engaged an increasing number of pediatricians, especially pediatric nephrologists. Finally, new antihypertensive drugs available for children have improved the management of hypertensive children. The growing interest in this topic is documented by a number of recent meetings and an expanding bibliography on juvenile hypertension [11, 49, 74, 84, 91a, 94, 100, 108, 120, 128].

Measurement of Blood Pressure in Children

Reliable techniques for blood pressure measurement are an important precondition for handling hypertensive children. Several factors have been identified to explain variations of blood pressure in the same child at different times. Some of these are intrinsic (e.g. circadian rhythms), while others are exogenous (e.g. induced by exercise). Taking simple precautions may reduce variations in blood pressure readings in children. Although the technique of blood pressure measurement today is fairly standardized in this age group, it is often difficult in clinical practice to follow proposed guidelines. The following guidelines, based mainly on European experience [94, 96, 109], deviate in some points from American guidelines [15].

Blood pressure measurements in children require a great amount of patience, especially in infants and toddlers. After the child is sufficiently relaxed, a resting time of at least 5 minutes should be observed before measurement. Although in most epidemiological studies children were examined in sitting position, in clinical practice the supine position might be preferred for measurements in young, restless children.

The two conventional non invasive techniques to determine casual (random) blood pressure in children are sphygmomanometry and oscillometry. Both require a cuff bladder that must be adapted to the size of the child [47]. If the cuff is too large, inappropriately low readings are obtained and vice versa. As a rule, the largest cuff that can comfortably be applied should be used, and its inflatable part should cover about $^{2}/_{3}$ of the upper arm's circumference. Usually a bladder width of 8 cm

is suitable for small children and a width of 12 – 14 cm (adult size) is required for older children and adolescents. Unfortunately, the commercially available cuffs for pediatric use are heterogeneous among different manufacturers [5].

In older children, *sphygmomanometry* is the method of choice. Auscultation of the first Korotkoff sounds corresponds to the systolic blood pressure, and disappearance of the sounds to diastolic blood pressure [84, 96]. If the value at the fifth phase is close to zero, although it rarely occurs, the measurement should be repeated. If this gives a similar value, phase 4 should be used [96]. In practice the difference between the figures obtained by accepting the two different phases is minimal.

Oscillometric methods by applying automatic devices (e.g. Dinamap) have become popular mainly in infants and small children because pulse detection by auscultation, as used in sphygmomanometry, is often troublesome [89]. Systolic and diastolic blood pressure is calculated by the device as a function of the mean arterial presssure, which is the point of maximal oscillation. Although oscillometric devices reduce observer bias, only a few instruments have been validated in children [61]. Measurements obtained by conventional sphygmomanometry and oscillometry should not be used interchangeably. At present, only limited normative blood pressure data are available in children. Therefore, further studies are needed before auscultatory methods can be eliminated [21]. The pediatric experience with other novel techniques to determine blood pressure noninvasively is still limited in children [130].

Noninvasive, repetitive blood pressure measurements over 24 hours, through the use of automated monitors, have also been successfully applied in children during normal physical activity [8, 15, 75]. *Ambulatory blood pressure monitoring* (ABPM) proved to be feasible and reliable, even in small children [40]. In many centers, it has become a standard procedure to follow children and adolescents with suspected or proven hypertension. Various types of automatic devices have been applied. Most pediatric experience is based on oscillometric monitors (e.g. SpaceLabs 90207). The main advantage of ABPM compared to casual blood pressure recordings is a reliable assessment of the circadian variations of blood pressure that appear to have prognostic significance, especially in patients with renal disorders [131]. ABPM also seems to be a sensitive tool to differentiate the determinants of primary hypertension and to detect early incipient hypertension in renal disorders [73]. The optimal method to evaluate rhythmicity of ABPM data is still debated.

Normal Blood Pressure Standards

In normal children there is a consistent increase of systolic and diastolic casual blood pressure with age, height, and weight [63]. Therefore, expression of blood pressure data in pediatric populations must be based on percentiles related to these variables. Full-term newborns have a mean systolic blood pressure of only 70 mmHg, which rapidly rises in the first months of life. In premature infants the rise of blood pressure levels is more rapid than in term infants [41]. The rapid rise of blood pressure during infancy and puberty (especially in males) seems to be related to increased growth and hormonal changes.

Combined material from many epidemiological studies performed in the US [84, 103] and Europe [31] provides representative

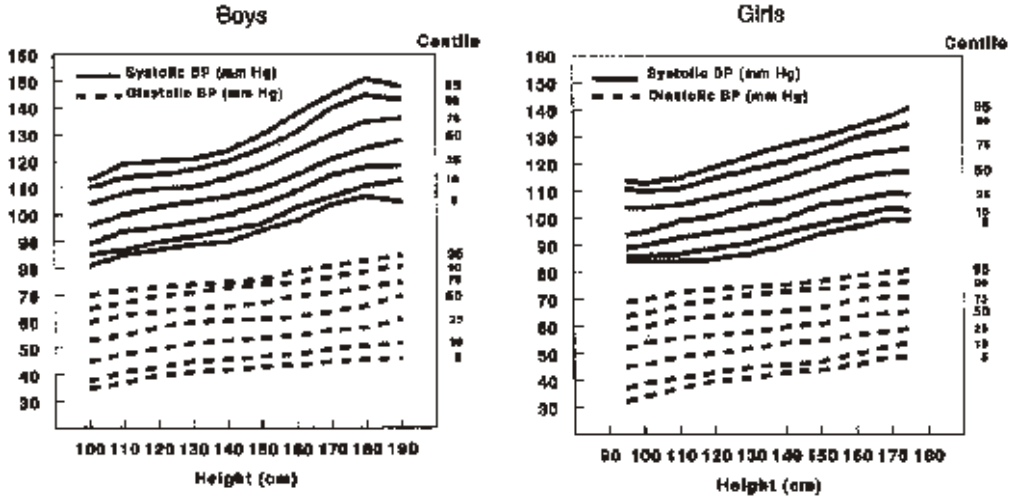

Figure 1. Height-specific percentiles of systolic and diastolic blood pressure in boys and girls. Adapted from de Man et al., J Hypertens 9: 112, 1991 [31]. Used with permission.

Table 1. 95th percentile of systolic/diastolic blood pressure (in mmHg) in North American boys and girls aged 3 – 16 years according to height percentile (extracted from [84]).

AGE (years)	BOYS 5th	BOYS 50th (median)	BOYS 95th	GIRLS 5th	GIRLS 50th (median)	GIRLS 95th
3	104/63	109/65	113/67	104/65	107/66	110/68
6	109/72	114/74	117/76	108/71	111/73	114/75
10	114/77	119/80	123/82	116/77	119/78	122/80
13	121/79	126/82	130/84	121/80	125/82	128/84
16	129/83	134/85	138/87	125/83	128/84	132/86

sex-related reference charts for casual blood pressure measured by sphygmomanometry in normal children and adolescents, although these are mainly based on cross-sectional studies.

For estimating a child's physiological blood pressure, body height appears to be a better indicator than age or weight [135]. Consequently, tall children are allowed relatively higher normal blood pressure values when related to height rather than to age. The European centile charts have related blood pressure to both age and height [31] (Figure 1). Recently pooled American data give the 90th and 95th percentiles of systolic and diastolic blood pressure by percentile of height [84] (Table 1).

Representative reference data for ABPM have only recently become available in children and adolescents [51, 97, 98]. A multicenter study from Germany provided height-related centile charts for daytime, nighttime,

Table 2. Oscillometric mean ambulatory blood pressure values in healthy children: summary for clinical use. Used with permission.

Height in cm (n)	Percentile for 24-hour period		Daytime percentile*		Nighttime percentile	
	50th	95th	50th	95th	50th	95th
Boys						
120 (33)	105/65	113/72	112/73	123/85	95/55	104/63
130 (62)	105/65	117/75	113/73	125/85	96/55	107/65
140 (102)	107/65	121/77	114/73	127/85	97/55	110/67
150 (108)	109/66	124/78	115/73	129/85	99/56	113/67
160 (115)	112/66	126/78	118/73	132/85	102/56	116/67
170 (83)	115/67	128/77	121/73	135/85	104/56	119/67
180 (69)	120/67	130/77	124/73	137/85	107/56	122/67
Girls						
120 (40)	103/65	113/73	111/72	120/84	96/55	107/66
130 (58)	105/66	117/75	112/72	124/84	97/55	109/66
140 (70)	108/66	120/76	114/72	127/84	98/55	111/66
150 (111)	110/66	122/76	115/73	129/84	99/55	112/66
160 (156)	111/66	124/76	116/73	131/84	100/55	113/66
170 (109)	112/66	124/76	118/74	131/84	101/55	113/66
180 (25)	113/66	124/76	120/74	131/84	103/55	114/66

* = Daytime 8 a.m. to 8 p.m., Midnight to 6 a.m. [123].

and 24-hour blood pressure obtained from more than 1100 boys and girls [123]. Compared to standards for casual blood pressure [31, 84] systolic daytime ABPM values increased only moderately with height; diastolic blood pressure remained almost the same, independent of height (Table 2, Figure 2). For systolic blood pressure the 95th centile of daytime values obtained by ABPM was higher than casual blood pressure in small children, but lower in tall European children. Diastolic ABPM values at daytime exceeded casual blood pressure by > 10 mmHg in the smallest height groups. The reasons for the variable results are not yet clear. Systolic and diastolic blood pressures recorded at night (from midnight to 6 a.m.) are 13 6% and 23 9% lower than blood pressure measured from 8 a.m. to 8 p.m., respectively [123]. For easier evaluation, these ABPM data may be expressed as SD scores after correction of their skewed distribution using a new statistical tool [140].

Definition and Prevalence of Hypertension

Many epidemiological studies in normal children tried to define a pathological blood pressure range, which is still debated [15]. Systolic and diastolic values below the 95th centile are considered as normal. Childhood hypertension is defined as (casual) systolic and/or diastolic blood pressure greater than or equal to the 95th centile, if confirmed by two further examinations [84, 96]. Blood pressure readings tend to decrease with repeated measurements in the same child, because children accommodate to the measure-

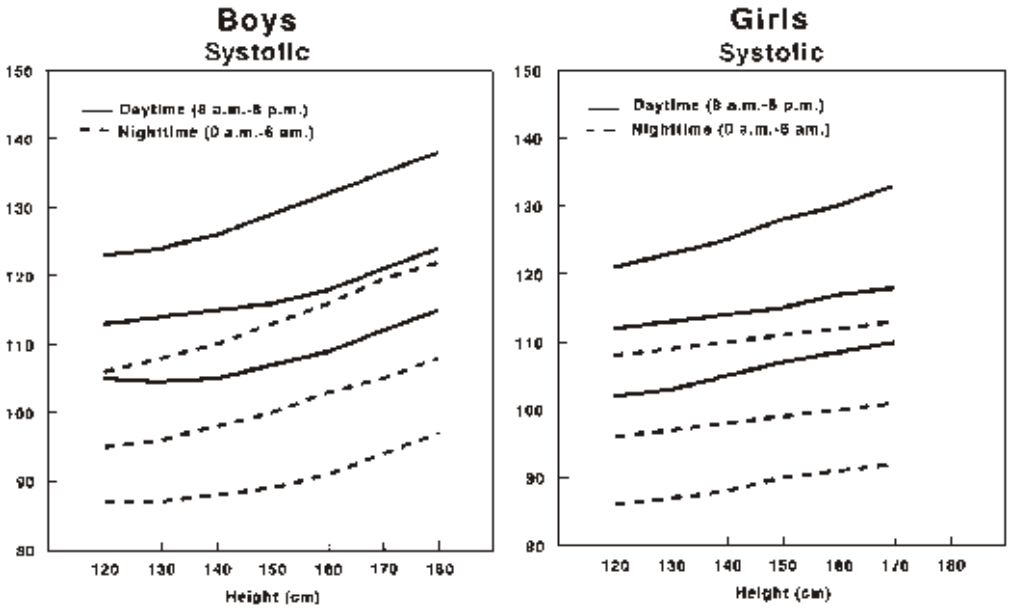

Figure 2a. Daytime and nighttime systolic blood pressure means related to height in boys and in girls for the 10th, 50th and 95th percentiles. Adapted from [123] p 180. Used with permission.

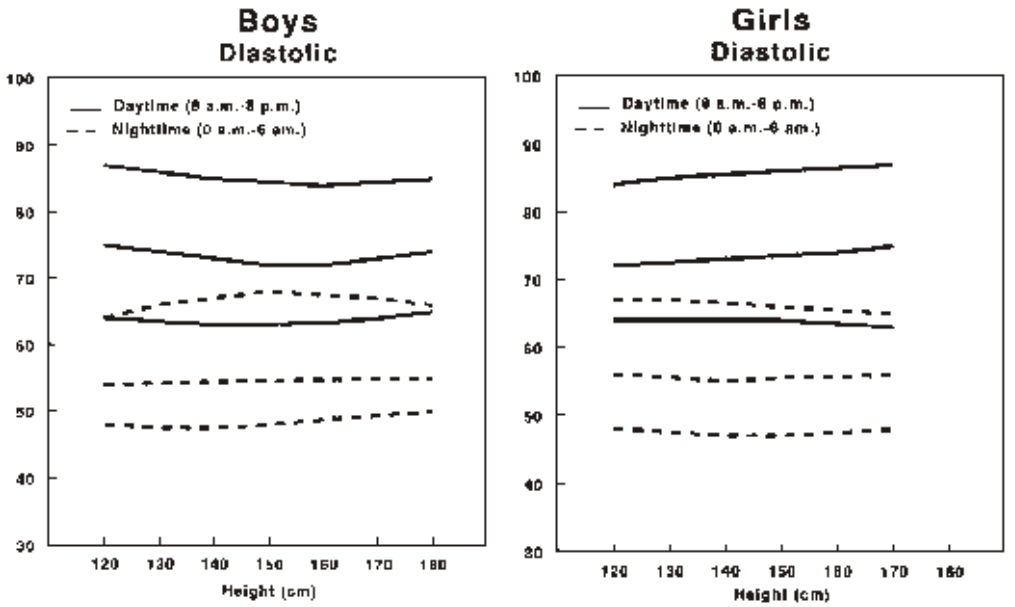

Figure 2b. Daytime and nighttime diastolic blood pressure means related to height in boys and in girls for the 10th, 50th and 95th percentiles. Adapted from [123] p 181. Used with permission.

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ment procedure and also because of the statistical phenomenon of regression towards the mean [120]. Therefore, only about 1% of the childhood population appears to have significant persistent hypertension, i.e. a blood pressure level above which medical evaluation and intervention are recommended. French researchers have defined established hypertension as a systolic and/or diastolic blood pressure 10 – 30 mmHg above the height- and sex-related 97.5th centile, if verified on three occasions. Values > 30 mmHg above the 97.5th percentile would correspond to immediately threatening hypertension [4]. For older adolescents an upper normal limit of 140/90 mmHg is usually accepted as normal. It is expected that in the future the application of ABPM and prolonged follow-up studies will allow a better distinction between normal blood pressure and clinically relevant hypertension.

Primary Hypertension

Early studies were chiefly centered on severe cases of childhood hypertension that usually are secondary to defined organ disorders. The concept was advanced that primary (essential) hypertension originates in childhood [14]. Although early mild essential hypertension poses little immediate risk to children, the findings of left ventricular hypertrophy (LVH) and hemodynamic changes are consistent with an adverse effect before adulthood [26]. Many epidemiological studies have demonstrated that the *initial* blood pressure of an individual child is the most powerful predictor of primary hypertension [129]. However, the tendency of blood pressure to "track", i.e., to remain within a given age-related centile over a longer period of time, is less marked in normal children than in adults. Tracking correlations of childhood (above 1 year of age) with adult levels of systolic and diastolic blood pressure range from 0.21 to 0.39 and from 0.11 to 0.50, respectively [65]. Therefore, a confident prediction of future blood pressure cannot be made for individual subjects, especially those in early childhood. Serial measurements over years might better identify children at risk for primary hypertension [10, 44], especially with respect to ethnic differences of blood pressure changes [30].

Except for age and body size, a number of other *determinants* of blood pressure have been identified in children that may influence the expression of primary hypertension: heart rate, gender, race, biological maturation (puberty), social class, genetic factors, nutrition, and some other exogenous factors [15, 129].

Genetic factors seem to play a major role in the determination of blood pressure levels during childhood [56, 114, 115]. Experimental investigations and numerous family, twin, and adoption studies have supported this concept. Family aggregation of blood pressure was especially convincing in a Minneapolis study which showed that pressure values of children were persistently higher in the presence of a family history of hypertension [83]. In addition, molecular genetic studies have supported the idea that primary hypertension has a hereditary background. Monogenic forms of hereditary hypertension apparently are rare (see Chapter I-20 by Luft F.C.: Essential Hypertension). Studies using markers adjacent to the renin locus and the angiotensin-converting enzyme (ACE) locus failed to find significant associations between blood pressure in siblings with primary hypertension, but possibly a link exists between the angiotensinogen gene locus and hypertension. Genetically determined mechanisms related to blood pressure control include erythrocyte membrane transport, kallikrein excretion, and the combined occurrence of hyper-

tension, hyperlipidemia, and insulin resistance (metabolic syndrome). Although recognition of the genetic determinants of blood pressure may help identify high-risk children, it is not yet a suitable tool for prevention of hypertension [44].

Among *nutritional factors* determining blood pressure levels, the impact of *salt intake* is still controversial in man [15, 118]. Various population studies have shown a relationship between salt intake and prevalence of essential hypertension. In populations with extremely low sodium intake from birth on (e.g. New Guinea), blood pressure does not rise with age and primary hypertension is virtually absent, as demonstrated by the International Cooperative Intersalt Study. Reduced exposure to salt during infancy in Western societies leads to an attenuated increase of blood pressure in the first 6 months of life. However, low salt intake in the first months of life has no influence on blood pressure levels at 8 years of age [56]. It appears possible, but has not been proven by epidemiological studies, that maintenance of low salt intake in older infants and children would result in a lower proportion of adults with primary hypertension [44]. Clinical trials with dietary salt restriction have so far been controversial in children and adolescents [15].

High potassium intake appears to protect against the development of hypertension in laboratory animals, while contradictory results have been reported from interventional studies in humans [70]. In a long-term observation of children aged 15 – 17 years extending over seven years, the slope of blood pressure increase was inversely related to the urinary excretion of potassium [39]. However, other epidemiological studies were not conclusive in attributing any role to potassium for blood pressure regulation in childhood [118, 122].

The same is true regarding *calcium intake*, although a recent investigation has demonstrated a small lowering effect on blood pressure by increased dietary calcium in preschool children [45].

The influence of *dietary fat intake* on blood pressure is controversial. Low fat intake and high ratios of polyunsaturated to saturated (P/S) fatty acids have been associated with low blood pressure in humans. However, an intervention study in healthy teenagers failed to confirm an effect of increasing nutritional P/S ratios on blood pressure [44].

Increased body fat (obesity) is one of the most important predictors of high blood pressure, especially when it involves the central compared to the peripheral compartment. Children with relatively high body size have elevated blood pressure levels compared to their slender peers. The Bogalusa Study showed a 5 – 7 kg increase in body weight in a cohort of normal children aged 7 – 9 years who were followed from 1973 – 1981 compared to a second cohort examined from 1984 – 1992 [42]. This relative increase in weight was associated with adverse changes in serum lipid and lipoprotein levels and with an increased final systolic blood pressure. It seems, therefore, that the secular trend toward obesity induces an exaggerated cardiovascular risk for adolescents. Factors contributing to the secular trend for relative obesity seem to be a more sedentary lifestyle and higher availability of food.

An influence of *maternal nutrition* on childhood blood pressure and later cardiovascular risk has been suspected because a correlation was found between the latter and maternal stature, birth weight, and placental weight. However, the absence of consistent relationships between social factors and blood pressure in the offspring provides little support for the hypothesis that maternal diet has an important influence on cardiovascular risk factors in childhood [138]. The fetal influences on adult blood pressure require further investigation [66].

Physical activity has long been claimed to reduce blood pressure. It is unclear if it acts only by reducing body weight. Studies in healthy preschool children do not confirm the favorable influence of physical activity in adults [60]. There is no doubt, however, that high physical activity in childhood predicts later activity in adult life with consequent benefits on cardiovascular morbidity.

Among *exogenous factors* related to hypertension, the role of alcohol consumption and smoking has not been clarified in adolescence. A British study found that the onset of smoking by age 10 or later was related to *low* diastolic blood pressure at age 10 [22].

Secondary Hypertension

The spectrum of secondary hypertension in children and adolescents comprises a large number of renal, cardiovascular, endocrine, central nervous system (CNS), and iatrogenic diseases [49, 128]. Up to the age of adolescence, secondary forms of hypertension prevail, while most adolescents present with mild essential hypertension.

Acute transient forms of secondary hypertension may be distinguished from chronic persistent forms. In both forms renal disorders predominate.

Transient Hypertension

Renal Disorders

Acute postinfectious glomerulonephritis (GN) is associated with initial hypertension in about half of pediatric patients [16]. Our own experience in 150 children with this disorder showed a prevalence of hypertension of 59% at onset with a rapid improvement within 1 to 2 weeks, resulting in a frequency of only 2% after 6 years of observation [110]. Hypertension is usually mild in idiopathic nephrotic syndrome responding to steroid treatment and associated with minimal glomerular lesions [62]. Transient hypertension is also frequently observed in other acute glomerular disorders, such as Henoch-Schönlein nephritis [139] and hemolytic-uremic syndrome (HUS). In vascular forms of microangiopathy associated with HUS, affecting mainly the medium-sized renal arteries, hypertension is more severe and more often persists compared to glomerular microangiopathy [50]. Various other disorders leading to acute renal failure (ARF) in infancy and childhood are accompanied by a transient rise in blood pressure, depending on the degree of renal dysfunction.

Nonrenal Disorders

Transient hypertension was described in children with increased intracranial pressure [59], convulsions, and other acute conditions of the central and peripheral nervous system [49]. Its pathogenesis is still poorly understood. Another unexplained type of juvenile hypertension was described after skeletal leg traction [52].

Chronic Persistent Hypertension

The prevalence of persistent secondary hypertension in children was estimated to be about 0.1% [68]. Table 3 lists the most frequent causes. In general, the younger the child and the higher the blood pressure, the

Table 3. Causes of persistent hypertension in children and adolescents.

1. Renal

Diseases of the renal parenchyma
- Glomerulonephritis: primary or secondary to systemic disorders (e.g. collagen diseases, Henoch-Schönlein purpura)
- Reflux nephropathy (renal scars)
- Obstructive uropathy (hydronephrosis)
- Hemolytic-uremic syndrome
- Polycystic kidney disease
- Chronic tubulointerstitial nephropathies (pyelonephritis, nephrophthisis etc.)
- Renal dysplasia

Renovascular
- Stenosis of renal artery and its branches (frequently combined with extrarenal vascular lesions)
  Primary: fibromuscular dysplasia, unknown histology
  Secondary: neurofibromatosis, thrombosis, aneurysm, arteriovenous fistula, aorto-arteritis, hilar compression, irradiation, post-trauma
  Syndromes of Williams-Beuren, Alagille, Ehler-Danlos, Klippel-Trenaunay, Marfan, Rett, Rothmund, pseudoxanthoma elasticum, tuberous sclerosis, calcifying arteriopathy
  Vasculitis: periarteritis, Kawasaki disease
- Renal vein thrombosis

Renal failure
- acute
- chronic

Other renal disorders
- Tumors (Wilms tumor, nephroblastoma, hemangiopericytoma)
- Toxic nephropathies
- Metabolic disorders (e.g. diabetes, hyperoxaluria)
- Post-renal biopsy, post-surgery

2. Cardiovascular
Coarctation
Patent ductus arteriosus
Arteriovenous fistula
Aortoarteritis (Takayasu disease)

Table 3. Part 2

3. Endocrine
- Pheochromocytoma
- Neuroblastoma, ganglioneuroma
- Adrenocortical disorders (see Table 5)
- Hyperthyroidism
- Hyperparathyroidism
- Turner syndrome
- Polycystic ovary syndrome

4. Neurologic
- Increased intracranial pressure (tumor, meningitis, trauma)
- Guillain-Barré syndrome
- Polymyelitis
- Dysautonomia (Riley syndrome)
- Psychic stress (anxiety)

5. Drug-related
- Corticosteroids, DOCA
- Erythropoietin
- Heavy metals
- Amphetamine
- Sympathomimetic drugs (nose drops, cold preparations)
- Tricyclic antidepressants
- Use of birth control pills
- Cyclosporine

6. Miscellaneous
- Bronchopulmonary dysplasia (in newborns)
- Intermittent porphyria
- Hypercalcemia
- Burns
- Cyclic vomiting with dehydration-related to leg traction (stretching of femoral nerve)

7. Primary (essential)

more likely a secondary cause of hypertension is present. In different series of children and adolescents reported with secondary persistent hypertension, disorders of the kidney predominate with 86% on the average, but distribution of different nephropathies varies considerably (Table 4).

Three groups of persistent renal hypertension may be distinguished: renal parenchymal

Table 4. Causes of persistent secondary hypertension in 1575 children and adolescents compiled from eight published studies [3, 6, 16, 31a, 43, 74, 133, 141].

Renal parenchymal disease	75.2%	(68 – 89)
Glomerulonephritis	28.1%	(13 – 50)
Pyelonephritic scars (with or without reflux)	23.0%	(10 – 33)
Obstructive uropathy (hydronephrosis)	10.0%	(0 – 18)
Hemolytic-uremic syndrome	5.0%	(0 – 16)
Polycystic kidneys	4.0%	(0 – 10)
Chronic tubulointerstitial nephropathies	1.0%	(0 – 6)
Other renoparenchymal disorders and renal tumors	4.0%	(0 – 10)
Renovascular disorders	10.6%	(0 – 20)
Coarctation	6.5%	(0 – 39)
Endocrine disorders	4.1%	(0 – 12)
Other disorders	3.5%	(0 – 8.5)
All persistent forms of secondary hypertension	(n = 1575)	100%

Most series include to a varying extent patients with preterminal renal failure and also some children on renal replacement therapy [43, 133]. The data are expressed as mean proportion of all children with persistent secondary hypertension (in parenthesis minimum and maximum proportion of patients reported from individual centers). The number of patients with primary hypertension reported from the same centers was 396, i.e. 20% (10 – 45%) of all forms of hypertension.

disorders, diseases of the renal vessels, and chronic renal insufficiency including transplantation. Various pathomechanisms have been proposed to explain transient and persistent renal hypertension, e.g. sodium and water retention (mainly in acute GN), vasoconstrictor mechanisms including the renin-angiotensin and sympathetic nervous system leading to renal ischemia as in HUS, and intravascular volume depletion resulting in the release of vasoactive hormones as in idiopathic nephrotic syndrome.

Renal Parenchymal Disease

Chronic GN, usually associated with the steroid-resistant idiopathic nephrotic syndrome, is responsible for about 30% of all cases of persistent renal hypertension if patients progressing to renal failure are included [16, 107]. Among the various histologic types, focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), and crescentic glomerulonephritis (CGN) most frequently lead to increased blood pressure. A high prevalence of hypertension is also observed in secondary glomerulopathies, e.g. in systemic lupus erythematosus (SLE).

A high proportion of pediatric patients with persistent hypertension is associated with chronic pyelonephritis, usually associated with *reflux nephropathy* and scars. After a follow-up of > 10 years, about 10% of patients with vesicoureteral reflux became hypertensive [117]. As shown by recent ABPM studies, blood pressure rises at an early stage of the disease [64, 90], but hypertension usually becomes manifest only in late childhood or adolescence in the presence of severe bilateral nephropathy and after reflux and urinary

tract infection (UTI) have already resolved (see Chapter I-13 by Arant B.S.: Reflux Nephropathy). The pathoanatomical and radiologic picture of scarring in reflux nephropathy associated with severe hypertension was described earlier as Ask-Upmark kidney [55] or as segmental hypoplasia [104]. It is characterized by segmental shrinking of renal parenchyma containing small, hyalinized glomeruli, dilated tubules, thickened and tortuous arterioles, and interstitial fibrosis. Usually, histologic examination does not determine whether these changes correspond to a congenital lesion or whether they are a result of scar formation from reflux or UTI in early life. The associated hypertension seems to be due to local renin secretion, although peripheral renin activity is often normal [57]. Genetic factors interfere in the pathogenesis of hypertension in reflux nephropathy.

Hypertension is also a feature of other forms of *urinary tract malformations*, especially in obstructive uropathy (e.g. ureteral stenosis). However, it appears that with earlier and improved diagnosis and treatment of these lesions in young children, the associated hypertension has become less frequent in recent years.

Polycystic kidneys (PKD) in children often present with an early increase of blood pressure before renal insufficiency occurs. Hypertension requiring drug therapy is found in 60 – 70% of patients with the autosomal recessive form of PKD (formerly called infantile type) and often becomes manifest already after the first year of life [143]. Interestingly, hypertension sometimes improves spontaneously. The autosomal dominant form of PKD (formerly called adult type) has a similar prevalence as the recessive form in childhood, but hypertension and renal insufficiency are less frequent. However, the application of ABPM reveals that blood pressure is increased in one-third of patients at a mean age of 12 years in the absence of clinical symptoms or a reduced glomerular filtration rate (GFR) [116]. To allow an early intervention, regular blood pressure monitoring is therefore recommended in these subjects.

Renovascular Hypertension

Renovascular hypertension is defined as hypertension resulting from lesions that impair blood flow to a part, or all, of one or both kidneys [18, 32, 54]. It represents about 10% of patients (20% of infants) referred to pediatric centers for persistent hypertension, and it more commonly affects young children (Table 4). Renovascular hypertension deserves special attention in childhood, because, except for aortic coarctation, it constitutes the most important cause of persistent hypertension amenable to surgical correction [126]. Considerable advances have been made in recent years regarding diagnosis and treatment of renovascular hypertension in childhood (discussed later).

The most frequent underlying abnormality is *renal artery stenosis* by fibromuscular dysplasia (70%). This affects primarily the media of the arterial wall leading to localized or extended narrowing of renal vessels that may be interrupted by aneurysmal sections. The disease is bilateral in about 70% of cases and may involve the main renal artery, peripheral branches, or both [32]. In a study in 54 patients with renovascular disease, main renal arteries were involved exclusively in 24% and intrarenal vessels exclusively in 44% [29].

The pathogenesis of fibromuscular dysplasia is unknown, but familial occurrence has been described, especially when associated with intimal hypoplasia and with autosomal-dominant *neurofibromatosis*. This condition seems to be the most prevalent ge-

netic disorder associated with renovascular disease [58]. In one series it was found in 15% of renovascular disease in children [18], but the true incidence is probably higher [91]. The gene involved (NF1) was localized to chromosome 17, and several mutations are known.

Renal artery stenosis has been associated with other inherited disorders or syndromes (Table 3). Some of these are combined with anomalies of extrarenal arteries, e.g. aorta, hepatic, or intracranial vessels [13, 29]. The combination with coarctation is known as middle aortic syndrome [127]. Renovascular hypertension is also induced by systemic vasculitis, unspecific aortoarteritis (Takayasu disease) [77], and other conditions listed in Table 3. Following renal artery thrombosis, it is mainly observed in newborns [2].

Chronic Renal Failure and Post-transplantation

Children and adolescents with chronic renal failure (CRF) and ESRD and after renal transplantation represent a growing group of patients suffering from hypertension [104a, 106, 113, 125]. In many pediatric series reporting on renal hypertension (Table 4), they are not clearly differentiated from patients with normal renal function. It is thereby often difficult to determine whether the hypertension is a consequence of the underlying renal disease or the result of renal insufficiency.

Frequency and severity of hypertension depend on the degree of renal failure, the nature of the primary renal disease, and the concomitant treatment. In an earlier study we found that blood pressure starts to rise at lower serum creatinine levels and is more severe in glomerular disorders, reflux nephropathy with renal scars, and polycystic disease than in renal hypoplasia or urinary tract malformations [107]. Practically all children and adolescents become hypertensive when their renal conditions approach end-stage.

In *chronic dialysis patients*, it is difficult to define hypertension precisely because of treatment-related fluctuations of blood pressure and possible changes of the day-night rhythm. In the first weeks or months after start of dialysis, blood pressure usually decreases, allowing a rapid reduction of antihypertensive medication [106], but in many dialyzed children and adolescents hypertension persists. According to EDTA data, 55% of dialyzed children in Europe received antihypertensive drugs with no difference between hemodialysis (HD) and peritoneal dialysis (PD) patients. Nevertheless, about one-third of all children had pressure levels > 10 mmHg above the 95th centile [76]. Determination of blood pressure by casual recordings fails to give consistent results in dialyzed children. The application of ABPM allows a more accurate measurement of interdialytic pressure. Using this technique, we found that hypertension is more prevalent in children and adolescents treated by PD than in those on HD (70% vs. 33%), while the day-night rhythm is conserved with both forms of treatment [71].

The two main *pathomechanisms* of hypertension in predialysis patients as well as those who have started dialysis are salt and water retention and stimulation of the renin-angiotensin system by renal ischemia and arterial damage. The first mechanism prevails in most oliguric dialysis patients when volume balance cannot be maintained, e.g. by reduced compliance with fluid restriction, which is a frequent problem, especially in adolescents. However, daytime blood pressure is not correlated with weight gain, suggesting that factors other than volume overload are involved in the hypertension of dialysis patients. In some patients (mainly with primary glomerular disorders), high renin secretion

from contracted native kidneys induces severe persistent hypertension. In such children, attempts to remove salt and water may paradoxically increase blood pressure in response to hypovolemia. A third pathogenetic factor of hypertension in dialysis patients is a stimulation of the sympathetic nerve activity [88]. It is notable that children exhibit a 2- to 4-fold increase in plasma noradrenaline and adrenaline during a HD or hemofiltration (HF) session [95].

After *renal transplantation*, hypertension seems to be more frequent in pediatric than in adult patients [17]. An American multicenter study found that 70% of young graft recipients require antihypertensive medication at 1 month and 59% at 2 years after grafting [9]. Similar findings were reported from Europe [76]. However, ABPM confirmed hypertension or normotension in only two-thirds of transplanted children and adolescents [72]. This and further studies also showed that the physiological nocturnal dip of blood pressure was attenuated in 30% of grafted pediatric patients, mainly in association with renal artery stenosis or chronic rejection and independent of GFR.

The pathomechanisms of post-transplantation hypertension are multiple [17, 24]. In the early phase, volume expansion, acute rejection crises, and treatment with high-dose glucocorticoids are the most important factors. Renal artery stenosis was reported in up to 20% of hypertensive grafted children [17] and seems to be caused mainly by vascular damage at the time of harvesting and by small vessel calibers in kidneys from young donors [53]. High renin release from native kidneys is less frequent. In later stages after transplantation, chronic rejection is the predominant etiology of hypertension. In addition, some studies found that immunosuppression by calcineurin inhibitors contributes to post-transplantation hypertension in children.

Endocrine Hypertension

Endocrine forms account only for 4% of secondary hypertension in children (Table 4). They present an important group because they are often amenable to surgery.

Pheochromocytoma in children is usually characterized by persistent hypertension and a high prevalence of extrarenal localization and multiple tumors [27]. The diagnosis is established by increased urinary excretion and plasma levels of catecholamines and their metabolites. We refer to Chapter I-23 (Sekkarie M.S.: Secondary Nonrenal Hypertension). To localize the tumor, ultrasonography and abdominal computed tomography (CT) are useful, if the tumor is large enough. Arteriography and venous catecholamine sampling (after adequate sympathetic blockade) are the most helpful techniques for localization. Metaiodobenzylguanidine (MIBG) scanning may yield false negative results.

Different *adrenocortical disorders* (usually inherited) are known to produce hypertension [49] (Table 5). They are generally characterized by renin suppression and hypokalemia. The hypertensive forms of congenital adrenal hyperplasia are associated with increased production of mineralocorticoids. Blood pressure is readily reduced by cortisol replacement [101]. Dexamethasone-suppressible hyperaldosteronism is an important differential diagnosis against the very rare Conn syndrome; low plasma renin activity (PRA) is an important marker [142]. In Cushing syndrome, an exceptional condition in children, cortisol production is increased by a tumor or hyperplasia. In the latter case, hypercortisolism is the result of stimulated ACTH secretion. Much more frequently, corticosteroid excess is due to high-dose administration of glucocorticoids.

Apparent mineralocorticoid excess and Liddle syndrome [134] are different forms of

Table 5. Adrenocortical forms of hypertension in children.

Disorder	Defect	Treatment
Congenital adrenal hyperplasia (adrenogenital syndrome)	11 -hydroxylase deficiency (deoxycorticosterone) or 17 -hydroxylase deficiency (17 deoxysteroids)	cortisol
Conn syndrome = primary hyperaldosteronism (tumor or hyperplasia)	aldosterone secretion	surgery, spironolactone
Dexamethasone-suppressible hyperaldosteronism (glucocorticoid remediable)	abnorma aldosterone synthesis, aldosterone excretion after ACTH	prednisone
Cushing syndrome (tumor or hyperplasia)	cortisol in Cushing's disease by ACTH	surgery, OPDDD
Apparent mineralocorticoid excess	11 -OH steroid dehydrogenase deficiency t/2 of cortisol serum aldosterone	dexamethasone, spironolactone, amiloride
Liddle syndrome	distal tubular sodium transport aldosterone	triamterene, KCl
Gordon syndrome (type II pseudoaldosteronism)	proximal tubular sodium transport	thiazides

(= increased production)

pseudohyperaldosteronism with autosomal dominant inheritance; clinically they are indistinguishable. Gordon syndrome is characterized by increased serum potassium levels, in contrast to the adrenocortical disorders associated with hypertension mentioned previously.

Cardiovascular Causes of Hypertension

Coarctation of the aorta is usually detected in infancy and is the most common cardiovascular form of hypertension. Characteristic findings are decreased blood pressure in the lower compared with the upper extremities, higher blood pressure in the right compared to the left arm, and a systolic ejection murmur over the back. The pathophysiology of hypertension in coarctation involves hormonal, renal, and mechanical factors. The diagnosis is usually made by echocardiography.

Other Forms of Hypertension in Childhood

A variety of lesions of the central and peripheral nervous system are associated with hypertension (Table 3). The pathomechanisms

are not well defined [49]. Sometimes systemic disorders or abnormalities that secondarily involve the central nervous system (CNS) induce hypertension (e.g. hypercalcemia). In adolescent females, hypertension may occur during pregnancy, is often associated with preeclampsia, and causes increased maternal and fetal morbidity and mortality. Care should be taken to avoid certain antihypertensive agents such as ACE inhibitors during pregnancy because of their toxic action on the fetus.

Among the drugs and environmental substances known to cause hypertension, glucocorticoids, sympathomimetic compounds, and tricyclic antidepressants are most important during the pediatric age. Their hypertensive action may be enforced by renal dysfunction.

Clinical Manifestations

In general, hypertensive children present less frequently with clinical symptoms and signs than do hypertensive adults. The clinical manifestations are age dependent. In infants common features are congestive heart failure (CHF), respiratory distress, cyanosis, feeding problems, vomiting, irritability, and convulsions [46, 68]. In older children hypertension is often silent and detected mainly on routine examination. Symptoms and signs are rarely found unless blood pressure is particularly high. They include headache, dizziness, nausea, abdominal pain, polydipsia, fatigue, cardiac failure, epistaxis, weight loss, and growth retardation. Many symptoms appear to be more the result of the underlying disease than of hypertension itself. Physical examination may reveal damage to target organs, notably the heart (functional and structural abnormalities, e.g. LVH) [112], kidney (proteinuria, hematuria), the CNS [111], and the retina. Sometimes it provides a clue for the etiology of hypertension, as in aortic coarctation (see above), or in the presence of abdominal masses (polycystic kidneys, renal or adrenal tumor), or of characteristic features of malformation syndromes associated with hypertension (Table 3).

Diagnostic Approach

The early recognition of hypertension in childhood requires regular measurements of blood pressure, even in asymptomatic children [96]. Once the diagnosis of persistent hypertension is clearly established, a careful history and thorough physical examination are required [31a]. The use of checklists and algorithms for the evaluation of hypertension is recommended [128]. The family history should include an inquiry on cardiovascular disorders, diabetes mellitus (DM), familial nephropathies, and some systemic disorders known to be associated with hypertension (e.g. phacomatoses). The patient's history should not only relate to actual symptoms of hypertension but also investigate back to the newborn period (asphyxia, umbilical catheter?). The use of potentially hypertensinogenic drugs (especially steroids, amphetamines, sodium-containing drugs, contraceptive pills) and substance abuse (smoking etc.) should be recorded. A dietary history (sodium, fat) may be contributory. Rapid weight gain or loss should be noted and its cause investigated. Further questions should be directed to systemic disorders and possible abdominal trauma.

Diagnostic studies need to be guided by the severity and persistence of hypertension. If blood pressure is > 10 mmHg above the 95th centile, the screening procedure outlined in Table 6 is recommended, independent of age

Table 6. Primary investigations proposed in children and adolescents with moderate and severe hypertension.

- Urine analysis: cells, protein, culture, vanillylmandelic acid
- Blood count
- Serum: creatinine, urea, electrolytes, plasma renin activity
- Abdominal ultrasound, including Doppler sonography
- ^{99m}Tc-DMSA or MAG^3 scintigraphy of kidneys
- Chest X-ray
- Electrocardiography
- Echocardiography
- Fundoscopy

adapted from [96]

and of the presence of clinical symptoms. If any investigation reveals an abnormality or if hypertension is severe, further studies are indicated that should focus on the organ involved (Table 7).

If a *renal etiology* is suspected, kidney function and imaging studies are required that are designed to differentiate renal parenchymal disease from renovascular disease. Ultrasonography and radionucleotide scintigraphy should be supplemented by color-aided Doppler flow studies to delineate the intrarenal vasculature [19]. Further imaging aids are urography, voiding cystourethrography, CT, magnetic resonance imaging (MRI), intraarterial (digital subtraction) angiography, and some more sophisticated meth-

Table 7. Supplementary investigations in hypertensive children and adolescents.

In case of suspected *renal* etiology:
- Glomerular filtration rate
- Intravenous urography
- Voiding cystourethrography
- ^{123}I-hippuran scintigraphy of kidneys under basic conditions and after captopril administration
- Renal angiography or digital subtraction angiography
- Renin sampling from renal veins and vena cava
- Computed tomography (CT) scan
- Renal biopsy

In case of suspected *endocrine* etiology:
- Plasma catecholamines, <u>if high</u>:
  - ^{123}I-meta-iodobenzylguanidine (MIGB) scan
  - vena cava sampling of catecholamines
  - urinary catecholamines
- Plasma aldosterone, <u>if high:</u>
  - urine mineralocorticoids
  - dexamethasone suppression test
  - adrenal scintigraphy

  <u>if low:</u>
  - urine mineralocorticoids
  - other plasma mineralocorticoids
  - cortisol response to ACTH or dexamethasone

In case of suspected *cardiovascular* etiology:
- Echocardiography
- Angiography or digital subtraction angiography
- Cardiac catheterization

adapted from [96]

ods [32]. As a screening for renovascular hypertension, the hypotensive response to oral captopril may be a suitable test [25], while the predictive value of the response of peripheral blood renin to captopril seems to be low in children [38]. Captopril (0.5 – 1.0 mg/kg) has also been used to unmask renal artery stenosis by increased radioisotope uptake, with a sensitivity of 80% in children [80].

Split renin sampling from renal veins is helpful for localization and evaluation of vascular lesions but is meaningful only in absence of antihypertensive therapy [32]. Preferably, angiography and split vein renal renin sampling are performed as a combined procedure, at least in young children, to avoid repeated general anesthesia. If nephrectomy is considered, an attempt should be made to determine the contribution of the affected kidney to total renal function by split renal clearance studies.

Prevention of Primary Hypertension

The preventive effects of early recognition and treatment of secondary hypertension in childhood appear to be limited because of the small proportion of patients involved. However, the prevention of *primary* hypertension in childhood has become a large-scale issue in public health.

Two strategies have been proposed for preventing primary hypertension in childhood [44]. The *population approach* attempts to modify the risks among all individuals of a population to achieve a moderate lowering of mean blood pressure by reducing cardiovascular morbidity. Within the population approach of prevention, an educational (active) and an environmental (passive) approach can be distinguished. The first is usually based on health education in schools by health professionals, mass media, and government programs and is practiced mainly in the US. At present, it seems to be the most promising strategy. It should involve family members and focus on physical activity and eating habits, prevention of obesity and smoking, and avoiding high salt intake. The environmental (passive) approach for preventing future cardiovascular disease does not require active steps on the part of the individual child. The efficacy of this method has mainly been proven by modifying the nutritional salt intake.

In contrast to the population approach, the *high-risk approach* concerns selected children with borderline hypertension who do not have a blood pressure high enough to require immediate treatment but may be destined to develop essential hypertension in adult life, especially in the presence of a positive family history or of an increased left-ventricular mass. Nonpharmacologic interventions proposed include weight reduction and increased physical activity. Some difficulties may be encountered when such an approach is followed strictly [44]. First, the precise identification of a high-risk child is difficult because the prediction of adult blood pressure from childhood values is not accurate with present methodology that applies rare casual blood pressure recordings. In future the use of ABPM or of reliable genetic markers of primary hypertension might improve the prediction. Secondly, the efficacy of early intervention strategies to reduce the risk of early cardiovascular disease in high-risk children has, in fact, not been clearly demonstrated, although it is expected that an intervention starting in childhood is more efficient than if delayed until adulthood. Finally, the cost effectiveness of a high-risk approach has been questioned. It should be comparable to screening programs for other disorders and

also to the population approach for preventing hypertension. Furthermore, wrong labeling of a child as being at a high cardiovascular risk could induce deleterious somatic and psychological effects. Therefore, the long-term benefits of intervention programs in high-risk children are considered to be modest [44].

Treatment

General Management

Hypertensive children and their parents need advice concerning diet and lifestyle. With mild hypertension, nonpharmacological forms of therapy will often be sufficient. The effect of a low-sodium diet or potassium supplementation on adolescent blood pressure is controversial [122]. Restriction of sodium intake may be reasonable, especially in salt-sensitive patients (e.g. those with renal failure) in order to spare antihypertensive drugs. Practical problems in reducing sodium intake should be handled in cooperation with a dietitian.

Weight loss is indicated in all obese children and adolescents with hypertension. It not only reduces blood pressure, but also salt sensitivity [99]. Regular exercise of the dynamic (aerobic) type seems to be appropriate unless hypertension is severe.

Pharmacotherapy

Long-Term Treatment

In view of the high morbidity and mortality, severe, sustained hypertension in children should generally be treated by antihypertensive drugs. Some authors believe that antihypertensive drugs are also indicated if blood pressure is only slightly above the 95th percentile. The individual decision to start pharmacotherapy should depend on the persistence and etiology of hypertension (early treatment in renal failure), the presence of other risk factors for cardiovascular disease (e.g. family history, hypercholesterolemia), and the concomitant involvement of target organs (e.g. LVH). In any case, nonpharmacologic forms of therapy should be considered before any pharmacotherapy is started. The goal of any pharmacotherapy is not only to achieve normotension, but also to improve the function of target organs and specifically to induce a regression of LVH.

Experience with antihypertensive drug therapy is limited in children and adolescents compared to adults [34, 48, 69, 91a, 119]. Study designs for testing antihypertensive medications in children have only recently been proposed [23]. In clinical practice, many drugs have been empirically found to be safe and effective in childhood although formal therapeutic trials in this age group are rare. The use of percentile charts of normal blood pressure is helpful for the management of hypertensive children.

Practical Approach to Oral Antihypertensive Treatment

Long-term therapy with antihypertensive agents generally follows a “stepped care” pattern, starting with a low dose of a given drug that is increased up to a tolerated maximum level and subsequently adding further drugs in a similar fashion until normotensive blood pressure levels are attained. Because a full effect is to be expected with most agents only after several days or weeks, a rapid change of the dose schedule must be avoided. With the introduction of more potent antihypertensive drugs with relatively few side effects, it is

Table 8. Dosage and side effects of oral antihypertensive drugs.

	Initial	Maximum dose in mg/kg/day	Interval (hours)	Side effects possible	Application in Renal Failure
Diuretics:					
Hydrochlorothiazide	0.5	2	12	Hypokalemia	–
Chlorthalidone	0.5	2	2 – 4	Hypokalemia	–
Furosemide	1	5	8 – 12	Hypokalemia	+
Spironolactone	1	5	8 – 12	Hyperkalemia	–
Triamterene	2	3			–
-andrenergic blockers:					
Atenolol	1	3	24	Bradycardia,	+
Metoprolol	1	4	12	hypoglycemia,	–
Propranolol	1	5	8 – 12	bronchospasm etc.	(+)
-blocker:					
Prazosin	0.02	0.5	8 – 12	Orthostatism	+
- and -blocker:					
Labetalol	1.5	10	12	Myopathy	(+)
Calcium antagonists:					
Nifedipine (sustained release preparation)	0.5	3	8 – 12	Flushing, tachycardia, peripheral edema, gingival hyperplasia	+
Vasodilators:					
Hydralazine	1	5	8 – 12	Flushing, palpitations, headache, fluid retention, lupus-like rash	+
Minoxidil	0.1	0.5	12	Hypertrichosis, edema	+
$_2$-agonist:					
Clonidine	0.005	0.03	8 – 12	Sedation	+
Converting enzyme inhibitors:					
Captopril	0.5	3	8 – 12	Leukopenia	(+)
In newborn babies	0.1	0.5	8 – 12	Rash, cough, loss of taste	
Enalapril	0.1	0.5	12 – 24	Decreased GFR, hyperkalemia	(+)

now often possible to control hypertension with monotherapy as in adult patients. However, as a rule a multiple drug regimen using low doses is preferable to a high-dose monotherapy accompanied by side effects. The initial drugs should be chosen individually on the basis of the actual blood pressure level, the pathophysiology of the underlying disorder, the side effects to be expected, and the personal experience of the treating physician.

The most frequently recommended classes of antihypertensive agents suggested for monotherapy are -adrenergic receptor blocking agents, calcium channel blockers, and ACE inhibitors. As a dual pharmacotherapy, the supplementation of a -blocking agent with a diuretic agent or a calcium antagonist has been successful in children.

Table 8 lists drugs used for oral antihypertensive treatment in children and adolescents,

initial and maximum doses recommended, and the most important side effects. A short description of the individual drug classes follows. For further pediatric information, the reader is referred to reviews on the subject [1, 34, 69, 91a, 119].

Supervision of antihypertensive treatment should include regular (initially daily) home measurements with documentation of blood pressure after adequate technical information of the patient or his parents and frequent medical follow-up visits, especially if therapy has been changed. With longer treatments, drug dosage needs to be adapted to body size and corresponding blood pressure norms. Noncompliance is an important problem, especially in adolescents, and is related to the use of multiple drugs and frequency of dosing.

Diuretics

The antihypertensive response to diuretics depends on their diuretic action, resulting in decreased extracellular volume, associated with a reduction in peripheral vascular resistance (PVR). Hydrochlorothiazide has been used most widely in children [81]. Its application should be restricted to patients with a GFR > 50 mL/min/1.73 m^2. The most important side effect is hypokalemia, which requires potassium supplementation. In some cases chlorthalidone may be preferable because of its prolonged action.

The loop diuretics are capable of inducing a brisk diuresis of greater size than other agents induce and are therefore indicated in patients with significant fluid retention. Furosemide given intravenously (IV) or orally (PO) is effective even in advanced renal failure, but its renal clearance is smaller in children than in adults [67]. It has successfully been applied in hypertensive children with acute GN. It is also useful as an adjunct to other antihypertensive drugs in patients with acute or chronic renal failure, especially if sodium restriction is difficult to obtain by dietary measures alone. Side effects are volume depletion, hypokalemia, and ototoxicity, which is often related to high blood levels during high-dose IV application. Furosemide-induced hypercalciuria may lead to nephrocalcinosis, especially in pre-term infants.

Potassium-sparing diuretics such as spironolactone and amiloride may occasionally be given to prevent hypokalemia. They also have a place in the management of adrenocortical forms of hypertension (Table 5).

-adrenergic Receptor Blocking Drugs (-Blockers)

The action of -blockers is complex and includes competitive inhibition of catecholamines on -receptor-mediated effects in heart, kidney, and the central nervous system. Cardiac output falls, the activity of the renin-angiotensin system is reduced, and the peripheral release of noradrenaline is impaired. Propranolol as a short-acting drug has been replaced in many pediatric centers by more cardioselective agents with a prolonged half-life ($t_{1/2}$), like atenolol, metoprolol, or acebutolol. Side effects are relatively infrequent in children. Resting bradycardia is rarely severe enough to withdraw the drug. Peripheral vasoconstriction may lead to Raynaud-like symptoms. In obstructive lung disease, -blockers may exacerbate asthmatic attacks, even when cardioselective agents are applied. In young fasting children, severe attacks of hypoglycemia have been described.

-adrenergic Receptor Blocking Agents (-Blockers)

The long-acting agent phenoxybenzamine and the short-acting phentolamine have a

place in the management of pheochromocytoma [27]. Prazosin and doxazosin, which have a high selectivity for $_1$-adrenoreceptors, may be applied in other forms of hypertension and are often combined with a blocker. Side effects are relatively mild.

Labetalol has both selective $_1$- and non-selective -adrenergic blocking activity and is used both PO and IV in children [20], mainly to treat hypertensive emergencies.

Calcium Channel Blockers

Calcium channel blockers inhibit the inward flux of calcium through voltage-dependent slow channels in cell membranes, resulting in vasodilatation. Pediatric experience was reported on verapamil [105], nifedipine [87, 93], nitrendipine [137], nicardipine, felodipine [132], and amlodipine [102]. For treatment of moderate forms of persistent hypertension, the long-acting preparations of nifedipine and nicardipine (given twice daily) are widely applied as monotherapy in pediatric patients. These agents are also useful in post-transplant hypertension, because they counteract the cyclosporin A-induced increase of blood pressure mediated by afferent arteriolar constriction. Side effects of calcium channel blockers (Table 8) are rare with sustained-release preparations and are usually limited to a short period after initial drug administration.

Other Vasodilating Agents

These consist of a pharmacologically heterogeneous group of agents that act on vascular smooth muscles to reduce PVR.

Hydralazine is still in use in some pediatric centers, although it is less effective than newer compounds and has many side effects. It should therefore be prescribed only in small dosages combined with a -blocking agent or diuretic.

Minoxidil is a strong vasodilator with similar side effects and with the additional danger of hypertrichosis 2 – 3 weeks after onset of treatment. It is therefore advocated only in hypertensive states resistant to other drugs.

Clonidine acts centrally as an $_2$-receptor agonist and may be given by the oral or percutaneous route. Although it frequently provokes sedation and a dry mouth it has proven useful in the treatment of sudden blood pressure elevation in chronic hypertension.

Angiotensin-converting Enzyme (ACE) Inhibitors

The introduction of ACE inhibitors has greatly facilitated the management of children with severe hypertension in recent years. ACE inhibitors interfere with the enzymatic conversion of angiotensin I to the active angiotensin II, a major vasoconstrictor and stimulus for aldosterone production. They are effective especially in patients with high plasma renin activity (PRA).

Captopril given orally decreases blood pressure within 15 – 30 min and reaches peak blood levels in 1 – 2 hours. It has a $t_{1/2}$ of only 2 hours in children [121], but its pharmacodynamic $t_{1/2}$ is considerably longer, which allows a dosage 2 – 3 times daily. Captopril, which has been extensively studied in children and adolescents [82], is particularly useful in newborns and infants in whom its potency is greater compared to older children [86]. Captopril treatment in this age group should therefore be started with only 0.01 mg/kg/dose, while in older children the recommended starting dose is 0.2 mg/kg, which can be increased up to 0.5 – 1 mg/kg/dose given 2 – 3 times daily.

Table 9. Antihypertensive drugs for hypertensive emergencies in children.

Drug	Dose
Nifedipine	0.3 – 1.0 mg/kg PO
Nicardipine	0.5 – 3.0 g/kg/min by IV infusion
Diazoxide	2 – 6 mg/kg rapidly IV
Labetalol	1 – 3 mg/kg IV
Clonidine	0.002 – 0.006 g/kg slowly IV or 10 g/kg/4 h by IV infusion
Hydralazine	0.2 – 0.8 mg/kg IV
Minoxidil	0.1 – 0.2 mg/kg PO
Sodium nitroprusside	0.5 – 10 g/kg min IV infusion (titration from lowest dose upwards every 20 min)
Urapidil	initial 1 – 4 mg/kg/h, reducing to 0.5 – 2 mg/kg/h by IV infusion

PO = oral, IV = intravenous

Enalapril and ramipril have a delayed action starting 1 – 2 hours and continuing for 18 – 48 hours after administration [79]. Therefore, these drugs are now preferred for long-term use in children [136] and are used also to reduce proteinuria [92, 124, 140a].

ACE inhibitors and their metabolites are excreted by the kidney, which requires a dose reduction in renal failure. The various side effects described previously with the use of captopril have become less frequent with reduced dosage and the introduction of long-acting preparations. Persistent cough still remains a problem in about 1% of patients. In the case of hypovolemia, ARF with hyperkalemia and renal artery thrombosis may develop due to the vasodilating action of ACE inhibitors on the efferent glomerular arterioles. Therefore, care has to be taken to avoid states of dehydration (e.g. by the use of diuretics). Before the start of any treatment with ACE inhibitors, renal artery stenosis should be excluded. Serum creatinine and potassium should be monitored frequently during treatment.

Clinical experience with the use of angiotensin receptor inhibitors (e.g. losartan, irbesartan) is still limited in children [36], and therefore these agents cannot yet be generally recommended.

Hypertensive Emergencies

Hypertensive emergencies are defined as a sudden increase of blood pressure (usually > 180/120 mmHg in older children) and are not regularly associated with clinical symptoms such as cardiac failure, headache, encephalopathy, facial palsy, or eye ground changes. Immediate intervention, even in asymptomatic cases, is important to avoid damage of target organs, especially the CNS [111]. It is debated if blood pressure should immediately be reduced to normal levels, because this might decrease brain perfusion [28].

Table 9 lists the recommended doses of antihypertensive drugs applied PO or IV to children with hypertensive emergencies. Oral nifedipine has become the drug of first choice in all pediatric age groups because it is effective, safe, and easy to administer [37, 93]. It is rapidly absorbed and reaches its maximum action after about 1 hour. In emergencies, the drug should be removed from the capsule either by having older children bite through the

capsule or by withdrawing its content and applying it by a syringe [119]. Sublingual administration, as formerly recommended, is not needed. If the response is insufficient, the initial dose may be repeated and possibly doubled. Recently, nifedipine has also been administered as an IV infusion (e.g. 5 mg/1.73 m^2 nifedipine given over 4 – 8 hours). The preparation is light sensitive. Frequent side effects of calcium antagonists are tachycardia and flushing of the skin.

As alternatives, IV boluses of diazoxide and labetalol [20] are recommended; however, they have more side effects. They are preferably given as continuous infusion [69, 119]. Clonidine has the advantage of also being applicable by the transcutaneous route.

In severe symptomatic cases of hypertension and in case of resistance to other drugs, sodium nitroprusside given as IV infusion is the drug of choice. However, it should be applied only under permanent monitoring of blood pressure, because this may rapidly drop to dangerous hypotensive levels. Side effects like vomiting and neurological symptoms are due to toxic metabolic products that accumulate, especially in children with renal insufficiency. As an alternative, infusions of urapidil have recently been recommended. Hypertensive crises due to sodium and water retention (e.g. in acute GN) are best treated by IV furosemide (2 – 5 mg/kg).

Surgical Treatment

Only a few relatively rare hypertensive conditions are amenable to a surgical treatment, including revascularization procedures. They include aortic coarctation, chromaffin and adrenocortical tumors, and different renal conditions. Surgical repair or balloon angioplasty of coarctation is frequently followed by an insufficient drop of blood pressure and may require additional drug therapy.

Unilateral nephrectomy is indicated in the case of a nonfunctioning kidney, that is, if the structure and function of the contralateral kidney are more or less intact as in the case of hydronephrosis or of a renal tumor. Recent studies have stressed the value of unilateral nephrectomy in various forms of renal hypertension [7]. After nephrectomy, it often takes weeks or months until the blood pressure normalizes, and pharmacotherapy must be continued in the meantime. Polar resection is sometimes indicated in presence of segmental renal scars.

Percutaneous transluminal angioplasty has become the first-choice treatment in short, isolated stenosis of the main renal artery and may be successful even in small children [85]. Long-term medical treatment over years is a suitable alternative in infants until they have reached an adequate size for surgery [12]. In bilateral and complicated cases of renal artery stenosis, other surgical techniques, including autotransplantation, have also been successful in children [33, 78, 126].

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Hemodialysis Technology

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Introduction

Hemodialysis (HD), the most prevalent treatment modality for end-stage renal disease (ESRD), has undergone tremendous evolution during the past decade, including mass production of highly efficient dialyzers, availability of sophisticated equipment to control fluid balance and deliver bicarbonate-containing dialysate, and an increase in the percentage of centers that re-use dialyzers. The use of high-flux dialysis has also increased since 1988, as represented by its use in at least 40% of the dialysis centers. The following describes these technologic advances, as well as recent developments in blood-membrane interactions and their clinical sequelae. Since familiarity with the physical characteristics of hollow fiber dialyzers represent an important issue in dialyzer choice, this chapter also provides a brief overview of the most important operating characteristics of hollow fiber dialyzers as well as the most important problems and appropriate solutions associated with their use.

Hollow Fiber Dialyzers

Physical Characteristics

Dialyzers provide a semipermeable surface across which a diffusion gradient is created between a patient's blood volume and a constantly repleted volume of dialysate. Hollow fiber dialyzers are chemically complex, having several compounds incorporated in their structural components: housing material, end cap compartments, potting material and transport surface. When clinical reactions occur, they may be due to material in the dialyzer assembly and not the components of the membrane [1, 2]. Reviewing the physical and chemical components of these units provide the clinician with a better understanding of dialyzer function and interpretation of clinical reaction to dialyzer use.

Geometry

The geometric characteristics of a hollow fiber determine the membrane surface area, which can be varied by changing the number of fibers, their length, and their internal diameter. Fiber diameter of currently available dialyzers varies between 190 and 220 μm, and fiber length between 185 and 270 mm. If fiber length is increased at constant fiber diameter and surface area, the number of fibers can be reduced. The increased length would increase shear rate and magnify the pressure drop. These 2 events have opposing effects: the increment in shear rate increases ultrafiltration, but the magnification of the pressure drop may imply that filtration equilibrium will occur before the end of the fiber. A substantial pressure drop occurs if fiber diameter is decreased. This would limit the ultrafiltration profile along the fiber and may also make

it more difficult to rinse the dialyzer free of blood at the end of the procedure. A critical minimal inner fiber diameter has been considered to be 180 μm. Fiber wall thickness varies depending on the nature of the membrane with synthetic fibers having thicker walls than cellulose-based fibers. Cellulosic membrane hollow fibers have undergone a progressive decline in thickness since their initial introduction because of their strength. This has led to an improvement in the clearance of small solutes and higher ultrafiltration rates. These features could be used to obtain high urea clearances with a smaller surface area, the latter being an important determinant of complement activation with some cellulosic membranes [3].

Blood Compartment Volume

Dialyzers have decreased in size since their initial development. This smaller size minimizes blood loss and stress on the patient's circulation. Since the late 1970's, there has been a 3-fold decrease in dialyzer weight and a 5-fold decrement in dialyzer total volume. The improvements in design and material have had a major impact on storage and cost. The blood compartment volume of currently used dialyzers varies between 18 mL in the pediatric size dialyzers and 150 mL in the largest adult dialyzers. Dialyzer blood volume is only a small fraction of the total extracorporeal circulation volume. The volume of blood in the dialysis tubing is usually larger than that in the dialyzers and varies between 160 and 270 mL. Thus, the size of the blood compartment of a dialyzer is not a critical factor in the choice of a dialyzer. However, the size of the configuration of the header and end-chamber may affect the ease of reuse and smoothness of blood flow in the dialyzer.

Blood Flow Distribution

In most hollow fiber devices, the fibers are potted in a tubular housing, which makes it easier to obtain a tight seal between the header and the housing. To assure even blood flow distribution, blood inlet and outlet are designed to allow the same blood velocity and pressure to be uniformly present in all fibers.

Dialysate Flow Distribution

Since the fibers in the bundle are not ideally spaced, and due to the nature of dialysate inlet/outlet designs, dialysate flow is not uniform over the entire membrane. At each end of the dialyzer, one can find conical sections (with the base at the end) where dialysate flow is reduced, being close to nil at the very ends of the fiber bundle. This implies that the active area for diffusion is smaller than the area for ultrafiltration. The longer a dialyzer is, the smaller the contribution of these low dialysate flow areas to the total surface of the fiber bundle. Nonuniformity of fiber arrangement can lead to dialysate channeling. One solution to the problem is to utilize separators between the fibers to optimize packing density. This can be achieved by either the use of "fins" on the outside of hollow fibers [4], or by insertion of a yarn weave prior to potting.

Housing Material

Blood comes into contact with the housing material in the inlet and outlet end caps. These are made of amorphous, rigid, and transparent material usually consisting of polystyrene, polycarbonates, or other polymers. They may be gas permeable, and polycarbonates can adsorb ethylene oxide (ETO) during the ster-

ilization process. The coloring of the end caps for inlet/outlet differentiation while useful in practical terms, interferes with the ability to examine the device at the end of the procedure for determination of the proportion of clotted fibers.

Potting

The function of potting material is to ensure a tight seal between the blood and dialysate compartments and to hold the hollow fibers. Potting material belongs to the polyurethane group which has a high affinity for ETO [5]. Further, the isocyanates used in the potting polymerization are haptens and can theoretically cause immunoallergic reactions. However, this has not been documented clinically [6].

Table 1. Membranes Used in Hollow Fiber Dialyzers

Cellulose Based
Regenerated Cellulose
Cuprophan
Saponified cellulose ester
Several varieties of regenerated cellulose
Modified Cellulose
Cellulose acetate
Cellulose diacetate
Cellulose triacetate
Synthetically modified cellulose
Hemophan
SMC
PAN-Regenerated cellulose
Synthetic Based
Hydrophilic by nature
EVAL C
EVAL D
Hydrophilic by process
Polycarbonate
PMMA
PAN (AN69,PAN-DX,SPAN)
Hydrophilic by blending
Polyamide
Polysulfone
Polyethersulfone/polyarylate (PEPA)

Membrane Materials

Dialysis membrane can be composed of one of four different materials: cellulose, substituted cellulose, cellulosynthetic, and synthetic (Table 1). The type of membranes can influence several aspects of dialyzer function including solute and water transport, sterilization methods, blood interactions, and other parameters. Cellulosic membranes remain to date the most commonly used membranes. According to the United States Renal Data Systems (USRDS) 1996 Annual Report, the distribution of dialyzer membranes used in the U.S. as of 1990/91, 64.6% of patients were dialyzed using an unmodified cellulose membrane, whereas in 1993 this figure had decreased to 41.8% [7]. Over the same time period, use of modified cellulose and synthetic membranes increased from 17.5 – 22.4% and 14.9 – 35.7%, respectively.

Cellulosic membranes are made up of a sequence of repetitive polysaccharide units containing hydroxyl groups, similar to bacterial cell walls. These membranes are highly hydrophilic and are associated with acute intradialytic leukopenia as well as complement activation. The development of substituted and synthetic membranes have resulted in membranes that are more biocompatible (see *Biocompatibility* p. 11). Substituted cellulose membranes are cellulose polymers with hydroxyl group substitutions (e.g. acetate, diacetate, and triacetate) making them more hydrophobic and more permeable to water

and larger solutes. Further development of synthetic cellulose membranes produced Hemophane, which has diethylaminoethyl (DEAE) radicals substituting 1% of the hydroxyl groups.

Synthetic membranes are non-cellulose based membranes and have decreased tensile strength compared to cellulose membranes. These synthetic polymers are grouped as "hydrophilic" (polyetherpolycarbonate) or "hydrophobic" (polyacrylonitrile-PAN, polysulfone-PS, and polymethylmacrylate-PMMA). In general the hydrophobic membranes are apolar, have low energy of interaction with water, adsorb proteins, are more porous and have high ultrafiltration coefficients.

The side group modifications on substituted/synthetic cellulosic membranes and the high adsorptive capacity of synthetic membranes leads to a decrease in the intensity of blood membrane interactions. The adsorptive property of these membranes may be a determinant of their biocompatibility (e.g. the PAN membrane can activate the complement system vigorously, but has a high adsorptive capacity for complement resulting in low net complement activation products that reach the systemic circulation).

Functional Characteristics of Hollow Fiber Dialyzers

Clearance is likely the most useful and important characteristic of a dialyzer, because it is a critical factor in determining the dialysis prescription. A wide range of clearances is available with significant overlap between dialyzer types and sizes that allows tailoring of the dialysis prescription to patient needs. The clinical importance of β_2-microglobulin removal by high-flux dialyzers remains to be confirmed by long-term studies [8].

Clearance

The definition of clearance as applied to hollow fiber dialyzers is identical to that utilized for the native kidney, namely the volume of blood completely cleared of a certain solute during a single passage through the organ or device. The calculation of clearance is similarly derived from a simple equation of mass balance: mass removed = mass at inlet – mass at outlet. Assuming a constant blood flow *(Q_b)* in the absence of significant ultrafiltration the above equation can be rewritten:

Mass removed = $Q_b[C_i] - Q_b[C_o]$ or
Mass removed = $Q_b([C_i] - [C_o])$

where *$[C_i]$* and *$[C_o]$* represent concentration of solute at inlet and outlet, respectively. Mass removed is by definition clearance times *$[C_i]$*, so the equation can be resolved into:

$$\text{Clearance} = \frac{Q_b([C_i] - [C_0]}{[C_i]}$$

Clearance can therefore be calculated from simple measurements of inlet and outlet concentrations and blood flow. Alternatively, in the case of dialysis or hemofiltration, clearance can also be calculated by measurement of actual solute removal (measurement of solute concentration in dialysate or filtrate factored by dialysate volume or flow rate). Given the variability and imprecise nature of both blood and dialysate flow rates, the actual collection of dialysate/filtrate over a defined period of time is likely the most accurate. However, for clinical purposes in HD, clearance by inlet/outlet concentrations is sufficient and is

relatively accurate for small solutes. For larger solutes, the degree of error may be more significant [9]. Clearance by the inlet/outlet methods does not distinguish between clearance into the dialysate and adsorption. This is particularly true for some middle size solutes, such as β_2-microglobulin, that are actively adsorbed by some membranes. For such solutes, measurement in dialysate underestimates clearance of the substance.

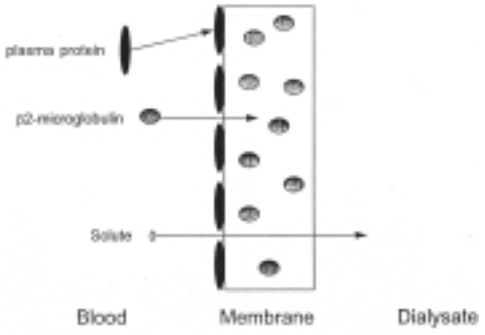

Figure 1. Model of interactions between proteins and hemodialysis membranes. Adapted from Leypoldt and Cheung, Artif. Organs 1996; 20:381-389, with permission.

Transport Mechanisms in Hemodialysis

The mechanisms of solute transport out of the blood during extracorporeal therapy are adsorption, diffusion, and convection. Although membranes have not been specifically designed for their adsorption characteristics, some membrane materials have the added benefit of removing some solutes by adsorption (e.g. β_2-microglobulin by synthetic membranes). In addition, some membranes bind activated complement factors to their surface [10] (e.g. cellulose acetate binds C3a and C5a) as well as adsorbing inhibitors for complement activation (e.g. Hemophane adsorbs factor H). Protein adsorption onto a membrane surface or within the porous structure of a dialyzer membrane can also affect solute transport.

A model proposed by Cheung and Leypoldt demonstrates how plasma proteins can interact with the membrane surface and affect the adsorption of other low molecular weight proteins and solutes (Figure 1) [11]. Binding of plasma proteins to the membrane does not result in significant changes in total protein concentration. In contrast, preferential adsorption of low molecular weight proteins (anaphylatoxins and β_2-microglobulin) can lower their plasma concentrations substantially. The pores of dialysis membranes that adsorb significant amounts of low molecular weight proteins are sufficiently large enough to permit intramembranous deposition. Presumably, these large pores also allow transmembrane transport of the low molecular weight proteins to the dialysate/ultrafiltrate compartment when the adsorption capacity of the membrane has been saturated or when the physicochemical properties of the protein do not favor its adsorption.

Diffusion across a semipermeable membrane is the primary mechanism for toxin removal by low-flux HD. The rate of diffusive transport increases with an increase in the concentration gradient across the membrane, the increase in the membrane surface area (*A*), and increase in the mass transfer coefficient (*Ko*) of the membrane times the surface area (*KoA*). Some augmentation of solute transport during HD may also occur with high rates of fluid transport (ultrafiltration) across the membrane, due to “solute drag”. Ultrafiltration adds to the clearance value, particularly for large solutes, as it is associated with further solute clearance through “convective transport” which is measured in terms of the sieving coefficient.

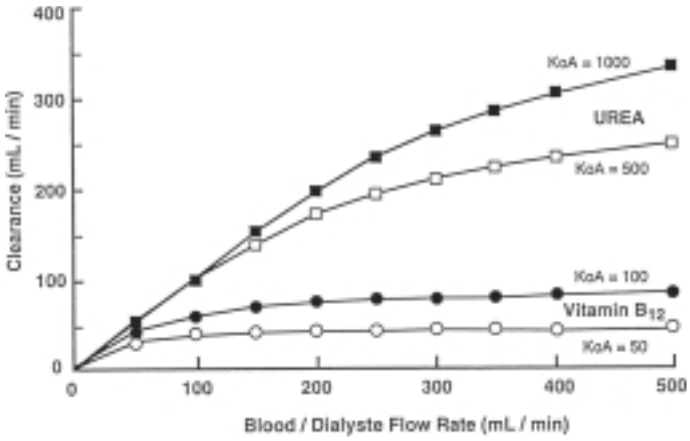

Figure 2. Dialyzer clearance of substances of different molecular weights as a function of blood/dialysate flow rate and the mass-transfer coefficient areas product (*KoA*). The clearance of large molecules (vitamin B_{12}) is not so flow-dependent as the clearance of small molecules (urea).

The sieving coefficient is the permeability of dialysis membranes to a particular solute and not its diffusability. The sieving coefficient is defined as the ratio of solute concentration in the ultrafiltrate to that of the plasma. The sieving coefficient remains near 1.0 for substances up to 1 kilodalton but is lower for larger molecular weight substances and reflect lower clearances via convection. Determination of solute sieving coefficients does not require accurate measurements of blood or dialysate flow rates. However, the sieving coefficient of a membrane may not accurately reflect its ability to remove a given solute if there is increased adsorption.

If a solute exhibits a high affinity for a membrane, it will be adsorbed with minimal transversing of the solute into the dialysate and the sieving coefficient will be low. As the membrane becomes saturated with the solute more will appear in the ultrafiltrate and there is an increase of the sieving coefficient. An example of this has been shown with β_2-microglobulin across the AN69 membrane during a hemofiltration session; this demonstrated a sieving coefficient of 0.06 that increased to 0.5 towards the end of the treatment [12].

Dialysate Flow Rates and Dialysis Efficiency

In a typical hollow fiber dialyzer blood flow and dialysate flow are arranged in a countercurrent format to allow for maximal concentration gradients between blood and dialysate at any point along the length of the fiber bundle. Flow in a concurrent direction, as may occur in error in connecting dialysate tubing, results in a 10% decrease in net solute flux. Clearance is directly related to blood flow rate within a definable range. The gain in clearance achieved by increasing flow rate is proportionally greater than that achieved by increasing dialyzer size. At low blood flow rates, for example, in continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodialysis (CVVHD) [13] the relationship between flow and clearance has a very steep slope and approaches linearity. The dependence is lessened at the higher flow rates used in modern clinical dialysis. As evident in Figure 2, for small solutes such as urea, the clearance increases with blood and dialysate flow rate, reaching a plateau beyond which no further increase occurs with increasing flow rate. However, for a large solute such as vitamin B_{12} (surrogate middle molecule),

the plateau occurs at much lower flow rates, and clearances are relatively insensitive to flow rates above this plateau limit. It is evident therefore, that while small solutes are *"flow limited"*, large solutes are *"membrane limited"*, with the limiting clearance being related to the *KoA*.

Both blood and dialysate form an unstirred thin layer on each side of the semipermeable membrane, which solute molecules have to cross before reaching the other side of the membrane. Increasing blood or dialysate flow helps diminish these unstirred layers. With dialysate, however, the major effect of increasing flow is to improve dialysate distribution in the fiber bundle which has a greater effect than diminishing unstirred layers. Any modest gain in clearance seen with increasing dialysate flow is due to improved dialysate distribution by eliminating the channeling effect (or nonuniform distribution).

The mass transfer coefficient (*KoA*) represents the ability of a solute to pass through pores of a dialyzer (i.e. the higher this value, the more permeable the membrane). The efficiency of a dialyzer is defined by its urea *KoA*. Conventional dialyzers have a *KoA* of < 300 – 400, while high-efficiency dialyzers have a *KoA* of > 600 – 700. In clinical practice, the most effective way to increase small solute clearance is to increase blood and dialysate flow rates. For increasing large solute clearance, however, the choices are to use a more porous membrane, a membrane with a higher surface area, a thinner membrane, or some combination of these approaches to increase the *KoA*.

Ultrafiltration and Ultrafiltration Coefficient

Fluid moves under hydrostatic pressure from the blood to the dialysate compartment (ultrafiltration). The quantity of fluid ultrafiltered depends on the pressure difference between the blood and dialysate compartments. This transmembrane pressure (TMP) can be controlled by varying the pressure in the dialysate or blood compartments. Increasing negative dialysate pressure will increase ultrafiltration. The plasma oncotic pressure opposes ultrafiltration. Thus, fluid moves only when TMP exceeds the plasma oncotic pressure. The ultrafiltration coefficient (K_{Uf}) is the number of mL of fluid transferred across the membrane per hour when 1 mmHg of TMP is applied. This value varies among different membrane types, with cellulosic membranes as a group having lower K_{Uf} values than synthetic membranes. However, with the versatility of cellulose-based membranes, alterations in the manufacturing process have allowed production of cellulose hollow fibers with high K_{Uf} values suitable for all clinical uses.

The flux of a dialyzer is defined by its K_{Uf}. High-flux dialyzers have K_{Uf} ranging between 20 – 60 mL/mmHg/hour, while low-flux dialyzers have K_{Uf} < 10 mL/mm Hg/hour and medium-flux dialyzers have K_{Uf} that range between 10 – 19 mL/mmHg/hour. High efficiency dialyzers and cellulosic dialyzers have K_{Uf} of 5 – 15 mL/mmHg/hour and 3 – 5 mL/ mmHg/hour respectively. In high-flux dialyzers, as the TMP increases, a plateau is reached with no further increase in water movement due to the concentration polarization of plasma proteins on the membrane. This creates a strong oncotic pressure opposing any further increase in water movement. As pressure in the blood compartment of the dialyzer almost always exceeds oncotic pressure, there is a certain amount of obligatory ultrafiltration associated with dialysis, which may have to be replaced by intravenous fluids in the occasional normovolemic or hypovolemic patient.

The relation between ultrafiltration and K_{Uf} can be expressed as follows:
Ultrafiltration = K_{uf} × TMP × dialysis time (in hours).

For example, if the clinician wishes to remove 4 L of fluid during a 4 hour dialysis using a dialyzer with a K_{Uf} of 5, the TMP should be adjusted to 200 mmHg. This will give a total ultrafiltration of 4 L (5 × 200 × 4). In practice, due to difficulties with accurate pressure measurements and variable K_{Uf}s of the same membrane under different conditions of use, it is often difficult to predict the exact amount of fluid that will be removed by the end of dialysis. Modern dialysis machines continuously measure ultrafiltrate, thus allowing for frequent adjustments and leading to more precise fluid removal. The published K_{uf} of a dialyzer is usually determined in vitro and is often an overestimate. In vivo, the K_{uf} may be decreased due to excessive protein layering, hematocrit (HCT) concentration, or fiber clotting.

Membrane Permeability

Membranes are also classified based on membrane permeability to middle molecules. There is general correlation between high water flux and high permeability to middle molecules (i.e. high-flux dialyzers tend to remove more middle molecules than low-flux dialyzers which are relatively impermeable). The Hemodialysis (HEMO) Study sponsored by the US National Institutes of Health has proposed that the β_2-microglobulin clearance be used to define permeability of dialysis membranes to middle molecules. According to this scheme, a dialyzer with β_2-microglobulin clearance < 10 mL/min is categorized as a low-flux (permeability) dialyzer, whereas one with clearance greater than 20 mL/min is classified as a high-flux (permeability) dialyzer. For a given high-flux membrane (e.g. one with a small surface area), the *KoA* of urea may be low (i.e. low efficiency). For a given low-flux dialyzer (e.g. one with a large surface area), the urea *KoA* may be high (i.e. high efficiency). Figure 3 demonstrates the general effect of “flux” and “efficiency” on removal of solutes with a wide range of molecular weights [14].

Red Cell Effects

Unlike studies in vitro with homogenous solute solutions, blood is a heterogenous fluid and solutes in it may be subject to compartmentalization between the fluid phase and formed elements. In addition, binding of solutes to formed elements or to plasma proteins may affect the component available for free exchange across a dialyzer membrane. For small molecules that are readily diffusible such as urea, the range of error between in vitro and in vivo clearance is small, on the order of 3% for variations in HCT within the clinical range [15]. Formulas to predict this effect for various types of dialyzers have been developed [16]. For other solutes however, particularly for protein bound solutes, the differences may be more substantial [17].

The almost universal use of recombinant human erythropoietin (rHu-EPO) in ESRD patients has led to questions regarding the influence of this patient factor on dialyzer performance. Investigations of the effects of increases in HCT on the clearance of urea by hollow fiber dialyzers [18] suggest that a change in HCT would alter only the blood side resistance. The modest contribution of the latter to overall resistance implies that a major change in blood side resistance (50%) would have only a minor effect on overall

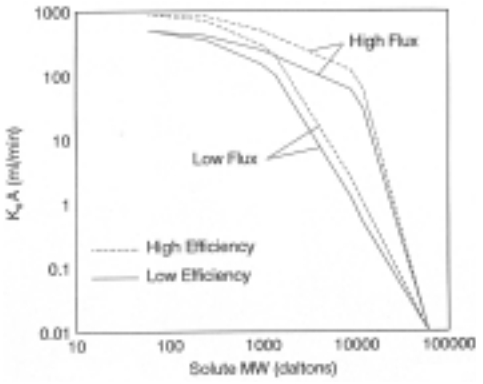

Figure 3. Theoretical *KoA* profile of high and low flux (permeability to middle molecules) dialyzers and high and low efficiency dialyzers. Adapted from Leypoldt and Cheung, Artif. Organs 1996; 20:381-389 with permission.

resistance (11%) and consequently on urea clearance (5%). For the clinically relevant range of variations in HCT (19 – 39%) there is little change in urea clearance.

Backtransport

Backtransport has been divided into backdiffusion and backfiltration [19]. The former is driven by the concentration gradient of a given substance and can occur in any dialyzer. Bicarbonate transfer from dialysate to blood is one example of therapeutic backdiffusion, whereas endotoxin transfer would represent an example of pathologic backdiffusion. Backfiltration is a convective phenomenon dependent on the presence of a pressure gradient directed from the dialysate compartment to the blood compartment. Backfiltration can occur in the setting of high-flux dialysis, as the pressure drop in the blood compartment along the fiber length dips below inlet dialysate pressure. This occurs under conditions of low TMP. Backfiltration almost never occurs under conditions of low-flux dialysis, and its occurrence during high-flux treatments depends on the transmembrane pressure used. Backfiltration is a crucial issue for device safety, because any contamination of dialysate or wash-out from the membrane can reach the blood side.

Hemofiltration and Hemodiafiltration

Hemofiltration

In hemofiltration, the ultrafiltrate flow through highly permeable membranes is augmented by increasing TMP and hydraulic permeability with absence of dialysate flow; ultrafiltration fluid losses are replaced by a substitution fluid, which is most often a modified Ringer lactate solution. The administration may take place either before (predilution) or after (postdilution) the hemofilter. Predilution requires substantially more substitution fluid than postdilution. The total volume of exchange for classic hemofiltration ranges from 20 – 40 L per treatment; the treatment typically carried out in thrice weekly sessions, each lasting 4 – 5 hours. The equipment for hemofiltration consists of the extracorporeal blood circuit, which has a geometric organization similar to that used in HD. In contrast to the complex hydraulic system required for HD, the hydraulic circuit in hemofiltration is markedly simpler.

The need for special equipment to allow hemofiltration to be performed safely, together with the high cost of replacement fluid, has limited the use of this technique to the management of acute renal failure (ARF) in critically ill patients with vascular instability.

Another major concern about hemofiltration is related to the fact that essentially large molecules are removed, and small-molecule removal is disappointing unless high volumes are ultrafiltered and substituted.

Hemodiafiltration

Hemodiafiltration combines the characteristics of conventional HD with hemofiltration, which permits increased clearance for middle and small molecules. This strategy may have a beneficial effect, not only on removal of molecules with a high molecular weight but also on removal of smaller molecules with substantial protein binding. At least for small protein-bound compounds, such as hippuric acid and indoxyl sulfate, superior removal by hemodiafiltration has been demonstrated compared to conventional HD. In contrast to hemofiltration, during hemodiafiltration only 8 – 15 L of replacement solution is used, which is infused into the venous return of the extracorporeal circuit. In general, an isotonic saline solution containing lactate as a buffer is used as a substitution fluid.

The life-sustaining aspects of HD and other deputative procedures described above should not obscure the fact that these treatments are merely an approximation of natural kidney function. None of these treatments accomplish any of the endocrine or metabolic functions of the natural kidney. Table 2 shows calculated convective solute clearances for various artificial kidney treatment techniques using the simple approximation that clearance equals the product of ultrafiltrate rate and sieving coefficient. In each of these therapies, the convective contribution to the solute clearance is only a small fraction of the weekly clearance of the normal native kidney. Finally, even though hemofiltration and hemodiafiltration with high-flux membranes permit high ultrafiltration rates and are efficient for removing β_2-microglobulin; nevertheless, albumin loss and perhaps other proteins should be taken into account when using theses procedures. Hemodiafiltration permits β_2-microglobulin removal and high *Kt/V*, and

Table 2. Convective Clearances as a Function of Ultrafiltration in L/Week as a Function of Sieving Coefficient in Various Forms of Artificial Kidney Treatment

	Therapy, UF/week				
Sieving coefficient	Low-flux HD 7L/week	High-flux HD 10L/week	HDF 30 – 60 L/week	HF 80 L/week	Native kidney 1,200 L/week
0.1	0.7	1	3 – 6	8	120
0.3	2.1	3	9 – 18	24	360
0.5	3.5	5	15 – 30	40	600
0.7	4.9	7	21 – 42	56	840
0.9	6.3	9	27 – 54	72	1,080

is probably the best way to treat chronic renal failure (CRF). Nevertheless, it is a very expensive procedure to perform in safe conditions.

Hemodialysis Membrane Biocompatibility

Blood-membrane Interactions

When blood encounters the HD membrane, several reactions are triggered including the complement cascade, the coagulation cascade, and the contact-phase pathway. In addition to these protein mediated pathways, evidence suggests that cellular mechanisms can also be activated during HD, both upon direct contact of cells with the membrane as well as by products of complement activation.

Complement Activation

During HD, complement activation proceeds via the alternate pathway. Among the different types of dialysis membranes, new cuprophane (CU) membranes activate complement to the greatest degree. The hydroxyl (OH) group on the surface of the CU membrane is thought to promote the deposition of C3b on the surface and the association of C3b with factor B (and subsequent activation of factor B by factor D) eventually resulting in formation of C3 convertase C3bBb and C5 convertase C(3b)nBb. There are several sequelae of complement activation including release of anaphylatoxins (C3a and C5a), formation of membrane attack complex (MAC), and activation of neutrophils and monocytes. C3a and C5a are potent, biologically active agents capable of producing intense vascular smooth muscle contraction, increased vascular permeability, and release of histamines from mast cells.

Although, CU membrane is a very potent activator of the alternate pathway, and has two OH groups attached to its glucan ring, substitution of 1% of these OH branches by DEAE residues (Hemophane) results in significant attenuation of complement activation. In addition, other membranes such as PAN and AN69 appear to activate complement system (locally), yet do not contain these OH moieties.

An alternate hypothesis for defining the complement activation potential of biomaterials has recently been proposed. Instead of defining an activating biomaterial as one that favors the deposition of C3b and the subsequent initiation of the positive feedback loop by C3bBb, the new hypothesis emphasizes the important inhibitory role of factor H. Thus, discrimination between activating and nonactivating biomaterial depends on the relative capacity of the surface to bind factor B or factor H. A membrane that promotes preferential binding of factor H (leading to inactivation of C3b and termination of the propagation of the complement cascade) and does not favor the binding of factor B has a low capacity to activate complement. Cellulose membranes have low affinity for factor H, an abundance of hydroxyl radicals, and little or no capacity to adsorb anaphylatoxins (C3a,C5a) and are therefore associated with the highest levels of complement activation.

Activation of complement is maximum at 15 minutes and lasts up to 90 minutes after initiation of HD with new cellulose-derived membranes. As HD proceeds, the rate of complement activation decreases. The mechanisms for this decrease have not been well-defined, but is thought to be due to coating of

the membrane with protein films [fibrin, albumin, C3 fragments, particularly C3b (covalently-bound) and C3c, C3d (non-covalently bound)]. For the same reasons, reused cellulose has a low complement activating capacity, a characteristic that may be beneficial to patients. It should be noted however, that reuse techniques which employ hypochlorite (in addition to formalin) remove the membrane coated protein, therefore abrogating the potential benefits of reuse. On the other hand, reuse with a mixture of peracetic acid/hydrogen peroxide also allows the surface of the membrane to become coated with protein which improves the membrane biocompatibility after repeated use.

Importance of Factor D

Factor D is the essential, rate-limiting enzyme of the alternate pathway of complement activation. Its molecular weight is 23 kilodaltons (kD), and its plasma concentration is increased approximately 10-fold in patients with ESRD due to impaired renal elimination. This high level of functionally active factor D is directly responsible for enhanced activation of the alternate pathway in the plasma of ESRD patients. In vitro and in vivo studies done by Pascual and colleagues using specific blocking antibodies against factor D have shown that blockade of factor D function achieves blockade of alternate pathway activation. It follows logically that adsorption of factor D on dialysis membranes could inhibit alternate pathway activation and plays an important role in the biocompatibility of PAN and PMMA membranes. In studies done by Pascual et al., there was a substantial decrease of circulating factor D in blood at the end of a HD session (80% with PAN/AN69 and 50% with PMMA, compared to less than 10% with cellulose acetate), with adsorption accounting for 98% and 85% of factor D removal by PAN and PMMA, respectively. No adsorption occurred on cellulose membranes [20].

Contact Pathway Activation

The contact pathway is activated by Hageman factor (factor XII). In particular, negatively-charged surfaces are potent activators of this pathway. PAN, with a negative charge of –153.9, induces a greater degree of activation of this pathway than the CU membranes (neutral charge). It is thought that the negative surface charge induces a conformational change of factor XII which promotes interaction between factor XII and pre-kallikrein, which is facilitated by surface-bound high molecular weight kininogen (HMWK). Once activated, kallikrein is potent in liberating bradykinin from HMWK.

Activation of Cellular Components

Neutrophils, monocytes, lymphocytes, red cells and platelets all are influenced by contact with the membrane. Activation of neutrophils leads to upregulation of adhesion receptors, release of proteinases and other intracellular enzymes, reactive oxygen species, leukotrienes, and platelet activating factor. Activation of monocytes leads to production of monokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF).

There are many potential consequences of repeated exposure of blood cells to surfaces capable of causing activation (Figure 4). Neutrophils are sequestered in the lung and other vascular organs. In addition, the ability of neutrophils activated by the membrane to respond to a secondary stimulus is significantly abrogated, and may leave the patient more susceptible to infection. When peripheral

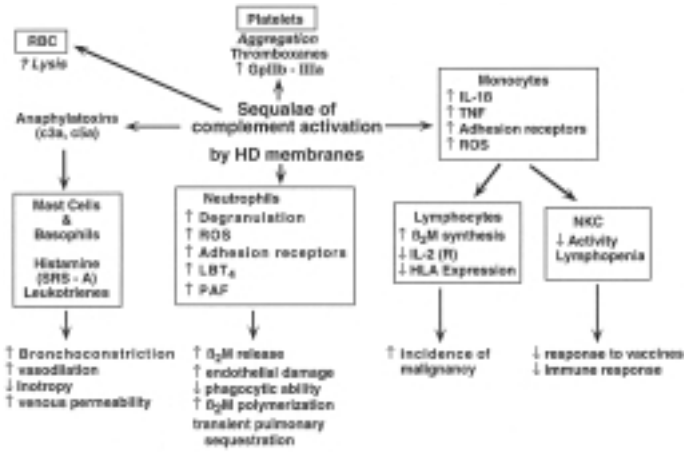

Figure 4. Sequelae of complement activation by hemodialysis membranes. (abbreviations per text details).

monocytes obtained during HD are lysed in vitro, their intracellular content of cytokines are found to be substantially elevated compared with monocytes obtained predialysis [21]. This observation suggests that peripheral monocytes are indeed activated even though they may not release their cytokines extracellularly during dialysis; these intracellular cytokines may eventually be released during the interdialytic period. These monocytes are chronically activated and have decreased ability to respond to stimuli such as endotoxin and phytohemagglutinin. Finally, the ability of peripheral blood mononuclear cells to express high-affinity IL-2 receptors, and the activity of natural killer (NK) cells have been shown to be reduced by the bioincompatibility of the membrane.

Although red blood cell (RBC) survival has been shown to be significantly reduced in dialysis patients, such a shortened survival has not been directly related to the biocompatibility of the dialysis membrane. Nevertheless, experience with the heart-lung bypass system has shown that complement activation, and specifically the release of the MAC (C5b-9) plays a major role in RBC membrane fragmentation and hemolysis.

Clinical Consequences of Bioincompatibility

The interactions of the dialysis membrane with the components of blood has the potential to lead to numerous clinical sequelae. In some areas, the evidence is supportive, but perhaps not conclusive. There are other areas in which membrane biocompatibility may play a role, but the available evidence is either based primarily on animal data or in vitro work. Areas in which the evidence is supportive include improved survival and recovery from ARF with biocompatible (BCM) compared to cellulosic bioincompatible (BICM) membranes, lower morbidity and mortality in patients on long-term HD using BCM as compared to patients dialyzed with BICM, and decreased incidence of infection, β_2-microglobulin (β_2M)-amyloid bone disease, and decreased catabolism. Areas in which potential sequelae of biocompatibility exist (but concrete human evidence is lacking) include the rate of loss of residual renal function, hypoxemia, pulmonary changes and decreased RBC survival.

Acute Reactions

"First-Use" Syndrome

A subset of patients receiving dialysis, estimated at 3 – 5% of the dialysis population, experience recurrent but less serious reactions to new CU membranes but not to their own used membranes. Reactions vary in severity, but usually consist of shortness of breath, chest tightness, back pain, as well as nausea, vomiting, and hypotension. Symptoms appear within the first 15 minutes of dialysis and are attenuated after 90 minutes. The first-use syndrome is the result of complement- mediated inflammatory processes. Patients who exhibit first-use syndrome have been shown to consistently activate complement (and therefore have very high levels of serum C3a desarginine) to a great degree in response to new cellulose membranes than do patients without this syndrome. In its most recent paper (1995), the Center for Disease Control (CDC) has determined that of all dialyzers sterilized with ETO, the cellulose based dialyzers are the ones associated with the highest frequency of first-use syndrome. The CDC also states that this association remains valid even after many of the patients who experience severe adverse first-use symptoms have been switched to gamma-ray sterilized dialyzers.

Anaphylactoid Reactions (AR) with AN69 Dialyzers

Several reports have described a high incidence of AR in patients dialyzed with high-flux membranes while simultaneously using angiotensin-converting enzyme (ACE) inhibitors. Many of these reports implicate PAN as the membrane most commonly involved in these reactions. A recent report that surveyed dialysis centers reporting AR showed that of 72 patients on a combination of ACE inhibitors but dialyzed with other membranes, and only 2 of 519 patients (0.4%) dialyzed with PAN membrane but not on ACE inhibitors developed AR. More recently, such reactions have been reported in patients on ACE inhibitors and dialyzed with PS and cellulose acetate membranes that have been re-used with Renalin.

The PAN membranes have been shown to generate high levels of bradykinin because they activate the contact-phase pathway vigorously. Kininase is an enzyme which degrades bradykinin. This enzyme is also inhibited by ACE inhibitors. The concomitant use therefore of PAN membranes and ACE inhibitors may lead to high levels of circulating bradykinins and adverse hemodynamic effects due to known physiologic effects of bradykinin (peripheral vasodilation, pulmonary airway constriction, and release of histamine from mast cells).

Acute Renal Failure (ARF)

Recently, the results of 2 prospective randomized studies have shown that the survival rate and the rate of recovery of critically ill patients from ARF were significantly higher when BCM were used compared to the use of BICM (CU). Schiffl et al. from Munich randomized 26 patients with ARF to low-flux Cuprophan membranes and another 26 patients to high-flux AN69 membranes [22]. The Cuprophan group required 35% more dialysis sessions, had longer duration before recovery from renal failure (22 days vs. 15 days), lower survival (35% vs. 62%, $p = .052$) and higher incidence of lethal sepsis (46% vs.

15%, p = .02). Hakim et al. compared 35 patients with ARF dialyzed with low-flux Cuprophan membranes with 37 patients dialyzed with low-flux PMMA membranes [23]. In patients without oliguria before the initiation of dialysis, the Cuprophan group had a higher incidence of developing oliguria (75% vs. 40%, p = .047), a lower probability of recovering from renal failure (40% vs. 85%, p = 0.003) and lower survival rate (40% vs. 80%, p = .01). However, no differences were recorded in the patients who had oliguria before the initiation of dialysis.

In a recent multicenter study comparing BCM and BICM membranes, significantly better survival and recovery from ARF with BCM patients, particularly in the patients without oliguria before initiation of dialysis was demonstrated. It was also shown that patients who recover renal function, the recovery occurred earlier in the group of patients dialyzed with biocompatible membranes. These results are of importance for critically ill patients with ARF, since the mortality rate in most series has remained around 60% despite an improvement in the general management of these patients.

Chronic Renal Failure (CRF)

There is no definitive evidence that patients on regular HD using BCM have a lower morbidity and mortality as compared to patients dialyzed with BICM. This is mainly due to the lack of well-designed, prospective and randomized studies that address these important issues. However, several non-randomized studies support the possibility that the use of BCM is associated with improvement in morbidity and mortality when compared to patients dialyzed with cellulosic membranes. Recent data from the USRDS confirms the reduction in the relative risk of mortality in long term HD patients dialyzed with non-cellulosic membranes. Hakim et al. analyzed prospective data on 2410 patients from the USRDS [24]. They found that patients dialyzed with synthetic membranes or substituted cellulosic membranes (acetate, diacetate, triacetate, and Hemophane) had approximately 25% reduction in relative risk of mortality compared with those dialyzed with regenerated (unsubstituted) cellulosic membranes, after adjustment for *Kt/V* of urea and comorbid conditions. However, this was not a randomized, controlled trial and the synthetic membranes tended to be high-flux, whereas the regenerated cellulosic membranes were low-flux.

Leypoldt et al. reanalyzed a similar subset of data from the USRDS [25]. Membranes were categorized according to their clearances of vitamin B_{12} as a marker of middle molecule removal. They found that, after adjustments for comorbidities, patient mortality correlated highly and inversely with calculated vitamin B_{12} clearance. This effect was independent of Kt/V.

Improvement in other features of dialysis treatment, such as increasing the delivered dose of dialysis or improving blood pressure control may mask or override, in part, adverse reactions to cellulosic membranes. One study from Tassin, France found that excellent patient survival can be obtained with cellulosic membranes if a higher dose of dialysis is delivered (24 hours/week, Kt/V=1.67) with an optimal control of blood pressure. This study has been cited as evidence that the type of dialysis membrane is irrelevant for clinical outcome. However, there is concern for selection bias with this study because of the exclusion of diabetic patients.

β_2-Microglobulin (β_2M)

In a large retrospective multicenter study of chronically dialyzed patients, van Ypersele de Strihou found that patients, treated with PAN/AN69 (as compared to CU membranes) had fewer radiological signs of dialysis-related amyloidosis (DRA). The difference in relative risk was clearly higher in older patients.

Although the precise mechanisms of amyloidogenesis are not completely understood, it must be noted that a "uremic concentration" of β_2M are a prerequisite for the development of DRA. It has been shown that the synthesis and release of β_2M are regulated by cytokines such as TNF, IL-2, and interferon γ and β. That BICM may increase β_2M production and accumulation in patients on regular HD is supported by studies which demonstrated an increased β_2M messenger RNA (mRNA) expression and production in lymphocytes and mononuclear cells cultured at the end of regular dialysis sessions with cellulosic membranes. Polymerization of this protein into amyloid fibrils might be enhanced by proteases and from complement-activated leukocytes. An additional factor in the propensity of patients dialyzed with cellulosic membranes to develop β_2M-amyloid bone disease may be due to the fact that most of the cellulosic membranes are low-flux membranes; these membranes do not have pore sizes large enough or an adsorptive surface to effect a significant clearance of β_2M from the circulation. On the contrary, removal of β_2M by PAN/AN69 is substantial (60% of total removal due to adsorption and 40% due to transmembrane passage). Removal of β_2M by high flux PMMA has been shown to be small and to occur mainly (more than 90%) by adsorption. Other membranes such as PS and polyamide have also been shown to possess adsorptive properties for β_2M, although less than PAN (adsorption of β_2M to PS membranes has been shown to represent < 20% of total β_2M removal, which occurs mainly by diffusion/convection). It should be noted that, although the removal of β_2M with membranes such as PAN and PMMA is important and permits a decrease of serum levels by 50% at the end of a normal dialysis session, it is still insufficient to compensate for the continued synthesis of β_2M (approximately 1500 mg/week). Nevertheless, a significant removal of β_2M during each dialysis may slow the continuous accumulation of β_2M in uremic patients. Overall, the potential benefits of synthetic membranes in preventing DRA may be predominantly related to decreased synthesis of β_2M by mononuclear cells rather than increased removal of β_2M. Equally important, these membranes by limiting repeated complement activation, cytokine production or protease release, may decrease the propensity to β_2M amyloidogenesis (β_2M polymerization or proteolysis).

Protein Catabolism and Malnutrition

Although the causes of malnutrition are multifactorial, there is increasing evidence that the use of bioincompatible membranes (BICM) contributes to malnutrition by eliciting acute catabolic effects during the dialysis procedure through vigorous activation of the complement system. The evidence of this catabolism was first shown by excess release of amino acid in normals and chronic HD patients exposed to BICM by Bergstrom and colleagues. Lindsay et al. have also shown evidence to support their proposal that for the same dose of dialysis, patients on a high-flux biocompatible membranes (BCM) had a higher protein catabolic rate (reflecting higher dietary protein intake) than patients on low-

flux BICM. Parker and Hakim have recently shown in a prospective randomized study a positive impact of the use of BCM independent of its flux characteristics on specific markers of nutrition and outcome. Recent data from the USRDS suggest an improvement in relative risk of mortality in patients using BCM compared to cellulosic membranes. The improvement was specific for infectious mortality and cardiovascular mortality, 2 causes specifically linked to malnutrition.

Infection

Uremic patients have enhanced susceptibility to infection due in part to impaired neutrophil function [26, 27]. Neutrophils eliminate bacteria through a series of carefully orchestrated events, including adherence to vascular endothelium, migration through the endothelium to the sites of infection, ingestion of bacteria, and killing the bacteria by the generation of reactive oxygen species and the release of microbial enzymes. There is increasing evidence that the HD membrane plays an important role in this enhanced susceptibility to infection [26 – 31].

One retrospective study compared the major causes of mortality in approximately 1000 patients before and after their HD membranes were changed from cellulosic to a biocompatible polysulfone membrane [32]. The most significant difference in the cause of death between these 2 time periods was in the incidence of infection, which was decreased by approximately one-half during therapy with the polysulfone membrane. Similar results were noted in another report in which the rate of hospitalization for infections in patients switched to a polysulfone membrane was one-half that in patients dialyzed with a cellulosic membrane [33].

Neutrophils from patients dialyzed with cellulosic membranes have a significantly attenuated metabolic response to phagocytic stimuli such as latex or zymosan when compared to neutrophils from patients treated with a polysulfone membrane [34]. During a follow-up of approximately 6 months, there was a higher incidence of clinically apparent infections in patients dialyzed with a BICM. Serum from patients dialyzed with BICM may inhibit the adherence ability of hematopoietic cells. As an example, one study found that serum collected from patients being dialyzed with cuprophane HD membranes significantly ameliorated the ability of granulocytes and monocytes to adhere to human saphenous vein endothelial cells [35]. No significant effect was observed with serum from patients undergoing dialysis with polysulfone HD membranes.

There is also evidence that lymphopenia and impaired natural killer (NK) cell function occur in patients dialyzed with BICM. Switching to a BCM can improve the lymphopenia [36] and NK function [30]. NK cells can spontaneously lyse target cells without prior sensitization; they are important in providing resistance to viral infection and destroying tumor cells. The impairment in NK function with cellulosic membranes may explain, in part, why HD patients have immune defects and an increased incidence of malignancy.

Dialyzer Reuse

Dialyzer reuse is the disinfection of a dialyzer for reuse by the same patient. Reuse has been utilized in chronic HD since the 1960's and has become the standard of care, albeit

amidst financial and clinical controversy. The development of reuse is the result of economic pressures from fixed reimbursement and increasing duration of dialysis therapy. The development of automated systems for reprocessing dialyzers has made the process more efficient and practical. Reuse has also provided a cost-effective means for widespread use of more expensive high flux/high efficiency dialyzers.

Epidemiology

Since 1982 there has been a steady increase in the number of centers and patients reusing dialyzers; 77% of dialysis centers and 83% of patients as of 1995 [37]. In the US, dialyzers are reused in 87% of non-hospital based dialysis units compared to 42% of hospital-based units, and in 87% of for-profit facilities compared to 56% of nonprofit units and 31% of government-owned units [38]. The average number of treatments a dialyzer can be used is approximately 13 with a maximum number of reuses around 30 [39]. The amount of financial savings by reprocessing dialyzers is substantial. With 5 manual reuses, a conservative estimate of savings has been set at $ 3,250/year per patient [40]. In the United States the estimated average savings per year with reuse is $276 million/year and a decrease in medical waste of 4,000 tons [41].

Automated vs. Manual Reprocessing

Dialyzers may be reprocessed manually or by using an automated device. Manual reprocessing is more labor intensive, results in variable quality control, and may result in fewer reuse cycles for an individual dialyzer vs. automated reprocessing. If performed meticulously, manual reuse is not associated with an increased incidence of pyrogen reactions vs. automated reprocessing [42]. Forty percent of US HD centers use manual reprocessing while the other 60% use automated equipment. Automated reprocessing devices may be single station (processing one dialyzer at a time) or multistation (multiple dialyzers simultaneously). The benefits for automated systems are:

- reproducibility of the reprocessing method,
- ability to perform dialyzer testing as a step in the reprocessing method,
- decreased risk of human error,
- assurance of the correct concentration of sterilant and adequate filling of dialyzer with germicide, and
- procedure documentation.

There are several reports that describe a decrease in the severity of first use syndrome with automated reprocessing vs. manual methods. One study with manual formaldehyde reprocessing showed 12 symptoms of first use syndrome (as described in the section on *acute reactions*), most notably for chest and back pain, were found to occur more frequently during the first use of a dialyzer than with following reuses [43]. In contrast, a separate study has shown that first use symptoms were eliminated using machine processed dialyzers. There were no differences in the incidence of symptoms between the first use of a machine processed dialyzer and subsequent reuses [44]. The differences between the incidence of first use symptoms (manual versus automated) may be explained by the following observations. New dialyzers contain particulate fibers of up to 1 mm in length, plasticizers leached from polyvinylchloride used in the manufacturing of dialyzer casing, and Limulus Amebocyte Lysate-reactive ma-

terial (LAL-RM) [45, 46]. No adverse clinical reactions have been attributed to intravascular delivery of particulates in dialysis patients, but plasticizers have been associated with cutaneous necrotizing vasculitis and hepatitis [45]. The reduction of symptoms during first use and subsequent reuse may be attributable to more rigorous pretreatment with machine processing (vs. manual) and the removal of particulate matter contained in the "dry pack" dialyzer.

Dialyzer Reprocessing

The steps involved in dialyzer reprocessing are summarized in Table 3 and briefly outlined below.

Table 3. Steps in Dialyzer Reprocessing

Assurance of AAMI water quality
Rinsing: Reverse ultrafiltration
Cleaning: Bleach vs. hydrogen peroxide
– Pressure leak testing
Performance Testing
– Total cell volume
– Clearance studies
– in vitro *Kuf*
Disinfection/Sterilization: Use of one of the following methods
– Formaldehyde
– Peracetic acid based germicides (e.g. Renalin)
– Glutaraldehyde
– Heat disinfection
Storage
Preparation for the next dialysis

Water Quality

When the recommended practice guidelines of the Association for Advancement of Medical Instrumentation (AAMI standards) for dialyzer reuse are followed carefully, disinfection of dialyzers or multiple use by the same patient is relatively safe and effective in eliminating infection, pyrogen reactions, and other potential complications associated with germicide use. Preparation of high quality water according to AAMI guidelines for the preparation of dialysate and filtration of dialysate can reduce the presence of bacteria and endotoxin by 99.9%. Water used to prepare disinfectional solutions should have a bacterial colony count of < 200 bacteria/mL and/or a bacterial LPS of < 1 ng/mL [47]. Bacteria and endotoxin contamination of water used to dilute disinfectant solution is one of the most common measures by which reuse related sepsis and pyrogenic reactions may occur.

Cleaning the Dialyzer (Bleach vs. Hydrogen Peroxide)

After reverse ultrafiltration of the dialyzer the next step in processing is cleaning the membrane. Sodium hypochlorite (bleach) diluted to ≤1% reduces the biocompatibility of BICM due to removal of coated proteins. There is also an increase in protein permeability of polysulfone dialyzers with repetitive bleach processing (see later section on increased protein loss with reuse). Hydrogen peroxide is another method for cleaning dialyzers. The use of hydrogen peroxide does not remove coated proteins so BICM become biocompatible with continued reuse but at the expense of ultrafiltering capacity.

Dialyzers that undergo cleaning with bleach can result in direct membrane damage. Pressure-leak testing is recommended to detect acquired membrane defects. A pressure gradient is produced by running pressurized air or nitrogen (at a pressure 20% above the maximal operating pressure) into the blood side of

the dialyzer or by subjecting the dialysate compartment to a negative pressure of 250 mmHg over 30 seconds [42]. A pressure change of < 0.83 mmHg/second indicates preserved membrane integrity. A pressure change < 1.25 mmHg/second for high-flux membranes is acceptable for continued membrane reuse.

Performance Testing

Total Cell Volume (TCV)

Dialyzers that are reused have decreased solute transport. This results from the number of occluded fibers, thickening of the dialyzer membrane, membrane pore occlusion and decreased membrane permeability. Monitoring of the TCV of a hollow fiber dialyzer provides a single method of detecting decreased solute clearance for a single dialyzer. The TCV is the volume of aqueous liquid needed to fully prime the blood compartment of a hollow fiber dialyzer. The TCV includes the fiber bundle volume and the dialyzer header volume. Measurement of TCV consists of an air or nitrogen rinse of the blood compartment using a compressible bulb with measurement of the amount of displaced liquid. Dialyzers having a TCV of < 80% of the original measured volume should not be reused. A TCV of < 80% represents an estimated decrease in urea clearance of approximately 10% [48].

Clearance Studies

In vitro urea, sodium chloride and B_{12} clearances may be determined for reused dialyzers. These measurements afford a more accurate means of assessing dialyzer clearance than TCV [42]. Protein and lipid components in blood, the level of the hematocrit, and incomplete red cell to serum equilibration of some substances during a single passage through the dialyzer blood compartment may reduce dialyzer clearance in vivo. In vitro clearances overestimate actual in vivo clearance. Clearance studies are not routinely performed on all dialyzers, but on a sampling basis, once yearly. A 10% loss of clearance in a reprocessed dialyzer is regarded as acceptable [42].

In Vitro Ultrafiltration Coefficient (K_{uf})

The K_{uf} of a dialysis membrane is the number of mL of fluid/hour that will be transferred across the membrane/mmHg pressure gradient across the membrane. The permeability of a dialyzer membrane to water is measured by determining the number of milliliters of water per minute (Q_f) passing through the membrane at a given pressure and temperature. Changes in the K_{uf} reflect changes in membrane surface area (occluded fibers) and membrane resistance (protein coating). The in vitro K_{uf} falls much less rapidly than the TCV because thrombosed fibers may still have high in vitro hydraulic permeability. This method may therefore overestimate the in vivo clearance of reused dialyzers, and close attention must be paid to expected and actual weight losses in the patient. Dialyzers are discarded when Q_f falls below 75% of the initial value [42].

Disinfection/Sterilization

Germicides

Disinfectant is run into the blood and dialysate compartments of the dialyzer, and the

dialyzer is capped and stored in a bag or container for 24 hours. Disinfectants currently used in reuse are formaldehyde, peracetic/acetic acid/peroxide mixture (Renalin), and glutaraldehyde. Formaldehyde was the most common germicide in use with manual reprocessing until the late 1980's. The advent of automated techniques and concerns regarding the toxicity of formaldehyde and potential injury to patient and staff has lead to increasing popularity of Renalin. In 1995, 57.5% of U.S. dialysis facilities were using Renalin, 37.9% were using formaldehyde, and 3.5% were using glutaraldehyde.

All germicides used in the reprocessing of dialyzers are biophysical hazards and have been implicated in clinical complications. Formaldehyde is the oxidation product of methanol and is rapidly oxidized in the body to formic acid and can be measured in normal human blood at a concentration of 2.5 parts per million (ppm) [49]. It is irritating to the eyes and airways in small concentrations of 0.1 – 5 ppm, causing tearing, coughing, and burning. Glutaraldehyde is 3 times more toxic than formaldehyde, with toxicity occurring in the range of 0.04 ppm. Peracetic acid or peracetic acid mixture (Renalin) has little vapor toxicity, but can cause skin burning on contact. In concentrated form it is chemically stable, but when diluted to clinical use concentrations it is less stable and requires monitoring to guarantee its germicidal effectiveness [50].

There is no standardization of the germicidal concentrations in dialyzer reuse. Formaldehyde concentrations vary from 0.5 – 4%, but it is most commonly used in the 2.0 – 2.5% range. When formaldehyde is used to disinfect dialyzers at room temperature, it should be used at a concentration of 4%, because this has been shown to be required for the effective killing of nontuberculous mycobacteria [51]. Renalin has been shown to be an effective disinfecting agent at 0.5% peracetic acid, but is most commonly used at the 3 – 3.5% concentration [50]. Renalin has been shown to be more effective in killing Bacillus subtilis and nontuberculous mycobacteria than 4% formaldehyde, which has resulted in gradually increased use by most dialysis centers.

Heat Disinfection

As an alternative to chemical (germicide) disinfections, heat disinfection has been developed for use with Fresenius polysulfone membranes in 1991. Heat disinfection has proven safe for patients and staff, easy to use, and environmentally friendly. All infecting agents, including spores, are destroyed by dialyzer reprocessing with heated water (100 – 105° C) for 20 hours. However, these temperatures may result in structural damage to the dialyzer, limiting reuse. Dialyzer reprocessing by using 1.5% citric acid heated to 95° C for 20 hours is an alternative method that produces equivalent microbiologic effects [52, 53]. Five years of experience at one center with heat at 95° C and 1.5% citric acid was associated with no pyrogen reactions or positive dialyzer blood cultures. Dialyzer performance as measured by kinetic *Kt/V* and measured urea clearance do not show significant changes with heat disinfection. In another center's experience, both small and large molecule clearances and the sieving coefficient for protein were insignificantly altered by the process. Whereas the procedure is relatively simple, quality assurance indicators are essential. This combination of heat and citric acid has proven to be safe and efficacious for disinfection with the number of reuses increased to 12 – 15, equal to the national average for other germicidal disinfection.

Advantages and Disadvantages of Reuse

Table 4. Advantages and Disadvantages of Reuse

Advantages
- Decreased intradialytic symptoms
- Decreased first use syndrome
- Increased biocompatibility
- Increased use of high-flux/efficiency dialyzers
- Decreased exposure to LAL-RM with first use of a dialyzer

Disadvantages
- Environmental exposure to chemical disinfectants
- Increased risk of clinical infections
- Pyrogenic reactions
- Infusion of sterilants and germicides: anti-N-AB formation/vascular irritation
- Decreased dialysis delivery: alteration of dialysis membrane integrity
- Increased protein loss/variation in β_2 micro globulin clearance

Decreased Intradialytic Symptoms

There is an overall reduction in the incidence of intradialytic symptoms in patients using new vs. reprocessed dialyzers. In a randomized double-blind crossover study comparing reprocessing with formaldehyde vs. patients using new dialyzers, there was a greater incidence of back and chest pain in patients using new dialyzers, whereas there was a lower but not statistically significant reduction of cramps, shortness of breath, nausea, vomiting, and nervousness in patients using reused dialyzers [54]. Another study has shown a reduction in the incidence of fever, sweating, respiratory distress, chest pain, nausea, vomiting, and hypotension in patients transferred from a unit practicing single use to a unit using formaldehyde reprocessed dialyzers [55]. More studies have been conducted using the more prevalent peracetic acid-hydrogen peroxide based germicides. One study reported fewer intradialytic symptoms using dialyzers reprocessed with peracetic acid when compared to formaldehyde [56]. Another prospective study has shown no difference in the intradialytic symptoms and changes in blood pressure between patients using new dialyzers compared to patients using automated-machine reprocessed dialyzers with peracetic acid-hydrogen peroxide based germicide [57].

Decreased First Use Syndrome and Improved Biocompatibility

Reprocessing of cellulosic dialyzers with formaldehyde, peracetic acid and glutaraldehyde results in improved biocompatibility of the dialyzer. Improved biocompatibility is thought to be related to the deposition of albumin, complement and fibrin on the blood compartment surface of the dialyzer. Protein residues coat hydroxyl ions of cellulosic membranes [58] and isolate the membrane surface from subsequent blood-membrane interactions. With reprocessing, C3b is firmly bound to the membrane and prevents further activation of the complement cascade [59]. This reduces the sequelae of complement activation, such as leukopenia due to pulmonary sequestration of leukocytes with resultant hypoxemia [60]. Activation of the kinin system, thromboxane production, histamine release and the production of various cytokines [61] may also contribute to the clinical syndrome of dialyzer bioincompatibility. Dialyzer bioincompatibility is restored with the use of bleach in the reprocessing process at high

concentrations (> 4%) due to membrane surface protein degradation. However, when lower concentrations are used (1%) with formaldehyde, biocompatibility is retained [62].

First use reactions (as described above in *Clinical Consequences of Bioincompatibility: Acute Reactions*, p. 14) are greatly reduced in patients using reprocessed cellulose dialyzers. When biocompatible membranes (e.g. cellulose acetate or synthetic membranes) are used for dialysis, there may not be a reduction in first use symptoms with reuse [63, 64].

Increased Risk of Clinical Infection

Dialyzer reuse has been associated with localized outbreaks of bacteremia and nontuberculous mycobacteria in centers where dialyzers are reprocessed. Most infections are a result of suboptimal concentrations of sterilant, such as the use of < 4% formaldehyde and inadequate mixing of Renalin [37]. Gram negative bacteria that occur naturally in water *(Pseudomonas, Flavobacterium, Acinetobacter, Alcaligenes, Xanthomonas, Serratia, Achromobacter, Aeromonas)* grow rapidly to levels of $10^3 – 10^6$/mL of water prepared by reverse osmosis, deionization, and carbon filtration. Contributing factors in the development of gram negative bacteremia are:

- suboptimal concentration of sterilant,
- inadequate mixing of germicide after dilution,
- variation in germicide concentration with manual reprocessing, and
- cross contamination of dialyzers by bacteria on technicians gloves. Another source of contamination is the replacement of inadequately disinfected headers and O-rings after these surfaces are removed for cleaning of residual blood products [65].

Highly resistant strains of non-tuberculous mycobacteria *(Mycobacterium chelonae, M. fortuitum, M. gordonae, M. scrofulaceum, M. avium, M. abscessus, M. intracellularis)* may survive and grow in processed and domestic water supplies. *Mycobacterium chelonae* has been found by a CDC survey to exist in the water supply of 83% of 115 surveyed centers and 50% of all water samples were positive for this organism [66]. These mycobacteria have been associated with outbreaks of septicemia and death in some reuse centers [67, 68]. Use of 4% formaldehyde is effective in killing nontuberculous mycobacterial as are carefully controlled solutions of peracetic acid and glutaraldehyde [37].

Increased Protein Loss/Variation in β_2-Microglobulin (β_2M)Clearance

Increased dialyzer membrane permeability can develop in some dialyzers undergoing repeated bleach reprocessing. This increase in permeability leads to increased losses of albumin and smaller proteins such as β_2-M. Protein sieving after the use of bleach as a cleaning agent and formaldehyde disinfection of polysulfone membranes was reported in 1995 [69]. Total protein and albumin losses were measured by total dialysate collection from 1 – 25 uses and compared with dialyzers processed without bleach for 8 – 25 uses. This study found that total protein losses were relatively small during the first 10 uses (1.5 – 3.6 mg/dL), but increased significantly after 15 – 25 uses (7.9 – 19.9 mg/dL). When multiplied by the total dialysate volume of 83 L, this represented protein loss of up to 20 g per dialysis. Albumin losses showed a similar increase up to 14.4 mg/dL after 23 – 25 uses. Dialyzers processed without bleach for similar numbers of uses had protein losses of 1.4

– 2.7 mg/dL and no measurable albumin. After removal of bleach from the reuse procedure, serum albumin concentration in the patients increased from 3.55 – 3.79 g/dL for the 6-month period before and after the change in the reuse procedure, respectively. In contrast to these findings, others have shown that in reused polysulfone dialyzers repeatedly exposed to bleach/formaldehyde reprocessing, albumin and protein losses into the dialysate were of smaller magnitudes; average albumin losses were 0.5 – 1.0 g during the 15th reuse [70]. In addition, others have detected, in the case of polysulfone dialyzers reprocessed with bleach, only minimal protein loss into the dialysate, in the order of 1 – 2 g per dialysis over 20 reuses. No loss or only a negligible loss was detected if the dialyzer had been reprocessed with peracetic acid or heat [71].

The effect of reuse on β_2M clearance is dependent not only on the type of reprocessing method but also the number of reuses and the membrane material used [72]. β_2M clearance by most currently available, first use, low-flux dialyzers is negligible (mostly < 5 mL/min) and does not change significantly with reuse. In contrast, β_2M clearance by first use, high-flux dialyzers of either cellulosic or synthetic origin can be substantial (often > 20 mL/min) [72]. Reprocessing without bleach does not sufficiently restore the membrane surface to its original state; the secondary membrane layer formed by the adsorbed plasma proteins tends to diminish the β_2M clearance of some membranes. In reprocessing methods employing the use of bleach solutions, the concentration of the bleach used and the time of exposure dictate the permeability of the membrane to β_2M and other proteins. Studies of polysulfone membranes using bleach reprocessing have shown that β_2M clearance remains constant or increases linearly. Increased β_2M clearance was determined in part due to the greater number of times a dialyzer was reprocessed (> 10) [73]. In contrast to polysulfone membranes, reuse with bleach does not alter β2M clearance of cellulose triacetate membranes [73].

Mortality and Reuse

The issue of mortality and reuse is a topic of continuous analytical research and clinical debate. The dictum of lower mortality rates seen in patients dialyzed with reprocessed dialyzers has been changed by 2 recent national studies [74, 75]. Both studies show, via different analytical methods, a higher risk of mortality with use of peracetic acid-based disinfectants in free-standing dialysis units. The original database for both studies consisted of 53,634 dialysis patients from 673 free-standing centers using reused, low-flux dialyzers, and 12,463 patients dialyzed in 184 free-standing centers using only single-use, low-flux dialyzers. In the first study [74] patients were followed for one year and the mortality rate was recorded. The results were as follows:

- patients in centers reusing dialyzers treated with glutaraldehyde had a 17% higher mortality than did patients in centers that did not reuse dialyzers,
- patients in centers reusing dialyzers disinfected with a mixture of peracetic acid, hydrogen peroxide and acetic acid experienced a 13% higher mortality than did patients in centers that did not reuse dialyzers, and
- patients in centers reusing dialyzers reprocessed with formaldehyde as the germicide had a mortality rate comparable to that of patients in centers that did not reuse dialyzers.

In the second study [75] incident rather than prevalent end stage renal failure (ESRF) pa-

tients were followed for 4 – 5 years. Neither of these studies were randomized and potential confounding variables were not considered.

In contrast to these results, data obtained from hospital-based outpatient dialysis centers showed that the mortality associated with reuse using any one of the three germicides (formaldehyde, glutaraldehyde, and peracetic acid) was not higher than that associated with single use. One theory to explain the difference between hospital based and free-standing units is that there is greater variation in adherence to AAMI practice guidelines in free-standing facilities than in hospital-based units.

Outcome results for dialysis units reusing high-flux dialyzers have been inconclusive because a comparable control group of units not reusing such dialyzers is not available. Compared with units that employ only single-use, low-flux dialyzers, the mortality risk for patients from reusing high-flux dialyzers has been favorable [74]. How to interpret these results is difficult given the major differences between these two modalities of dialysis.

Water Treatment

Recent technological advances in dialysis practices including high flux and high-efficiency dialysis, ever-increasing dialyzer reuse, and bicarbonate dialysate have heightened awareness about the safety of dialysis water. Fortunately, the aforementioned dialysis practices have been paralleled by continuous advancement in reverse osmosis membrane technology. Reverse osmosis membranes represent an effective barrier to endotoxin and bacteria with clear benefits over simple deionization.

Essential Components of Water Purification

The efficiency of a water purification system depends on the capacity of the system, the nature of the incoming water supply, seasonal variations in municipal water quality, and the desired quality of the water product. Table 5 lists the components, advantages, risks, and AAMI recommendations for users of HD water treatment systems. Fluoride contamination is reviewed by Mujais and Ismail in the chapter on “Complications During Hemodialysis”.

Chloramines and Carbon Filtration

Most adverse events related to a chemical toxin in the water supply are due to chloramines. Chloramines can pass readily through dialysis membrane and cause oxidant damage to red blood cells (RBC’s) (hemolysis). Most episodes of chloramine toxicity stem from ever-changing nature of municipal water supplies. Water can contain naturally-occurring organic substances, such as humic acid, that react with chlorine to form trihalomethanes. Trihalomethanes are carcinogenic, and in 1979 the Environmental Protection Agency (EPA) ruled that their level in drinking water supplies should not exceed 0.1 mg/L [76]. Chloramines are an effective alternative to chlorine since they are more stable and maintain bactericidal activity at lower total chlorine concentrations. Removal of chloramines from water can be achieved only by carbon adsorption or the addition of ascorbic acid to

Table 5. Components, Advantages, Risks, and AAMI Recommendations for Users of Hemodialysis Water Treatment Systems

Component	Advantages	Bacterial proliferation (Other risk)	AAMI recommendations
Sediment filters	Removes particulate matter	+	Opaque housings Pressure gauges, pre and post filters Monitor pressure drop (ΔP) Change filters when $\Delta P > 10$ psi Monitor for bacteria
Water softener	(1) Removes calcium and magnesium (2) Protects against scaling of RO system	+	Automatic regeneration with "bypass" Use pellet salt designed for softeners Check timer before dialysis Check hardness before dialysis
Carbon filters	Absorbs chlorine and chloramine	+	Use disposable carbon (GAC) Use 2 GAC tanks in series Each GAC tank with EBCT of 3-5 min 5μ filters downstream Monitor for exhaustion; replace exhausted tanks (backup system replaces spent tank when chloramine level > 0.1 mg/L) Monitor for bacteria
Reverse osmosis	(1) Rejects univalent and divalent ions (2) Filters bacteria	+	Must produce AAMI quality water Audible/visual alarms Monitor salt passage (2 × initial) (Salt passage = 100-rejection rate) Monitor pretreatment
Deionization	Removes all types of cations and anions	+	Continuously monitor resistivity (< 1 mΩ/cm) Temperature compensated monitor Visual and audible alarm GAC upstream Don't use industrial or process resin
Disinfection	Prevention of endotoxemia and pyrogenic reactions	Anti-N-like antibody formation (formaldehyde) Anaphylactoid reactions (ACE inhibitor/Renalin/reprocessing)	4% formaldehyde, 24 hours contact time 1-2% formaldehyde, 40°C, 24 hours Renalin/diacide

GAC: granular activated carbon GAC; EBCT: empty bed contact time; maximum mesh size 12 × 40 and minimum iodine number of 900; ACE: angiotensin-converting enzyme; RO: reverse osmosis

the water [77]. These processes have a finite capacity for chlorine removal due to variation in the source of the carbon and due to fluctuations of the chloramine concentration in the public water supply.

Granular activated carbon (GAC) will absorb chlorine, chloramines, and other organic substances from water. Since carbon filters are highly porous with a high affinity for organic material, they can be contaminated with bacteria if they are not serviced properly or exchanged frequently. The size of an activated carbon bed requires an understanding of empty bed contact time (EBCT). The EBCT is calculated as

EBCT = [V] [7.48 (gallons/cu. ft.)]/Q, where V = volume of carbon required in cubic feet, Q = water flow rate (gallons/minute).

The recommended EBCT for chlorine removal is 6 minutes and, for chloramine removal is 10 minutes.

The FDA recommends that 2 tanks filled with GAC be used in series. Each tank should have an EBCT of 3 – 5 minutes. When the first GAC filter has a chloramine concentration in the effluent filter > 0.1 mg/L, it should be replaced within 72 hours. Similarly, if the chloramine level in the effluent of the second tank exceeds 0.1 mg/L, the water must not be used for dialysis.

Aluminum Toxicity and Reverse Osmosis

In the early 1970's, aluminum toxicity was first described by Alfrey and colleagues in Denver [78]. This syndrome was characterized by speech abnormalities, myoclonus, personality changes, seizures, and progression to death within a few months [78]. Extensive studies revealed that patients with the syndrome had high levels of aluminum in organs such as the brain and bones [79, 80]. Further investigation revealed that the syndrome occurred in areas with high aluminum in the municipal water and that the increased body burden could be accounted for by transfer of aluminum from the dialysate to the blood [81, 82].

Aluminum is commonly added to municipal water supplies as a flocculating agent. In aqueous solution, aluminum exists in cationic form at acidic pH and in anionic form at alkalemic pH; at neutral pH it is present mainly as colloidal aluminum [83]. Due to its chemical properties aluminum is poorly removed by softeners and ion exchange at neutral pH. The development of reverse osmosis in the 1970's provided for a mechanism of water purification and aluminum removal from dialysate.

Reverse osmosis applies the principles of high hydrostatic pressure across a semipermeable membrane to a solution to prepare a purified solvent. This process rejects 90 – 95% of univalent ions (e.g. Na^+), and 95 – 99% of divalent ions, as well as microbiologic contaminants. Accordingly, 2 – 10% of the dissolved ions will pass through the membrane into the product dialysate water. Aluminum is well rejected by reverse osmosis membranes over a wide pH range and is the method of choice for water purification. Reverse osmosis generally produces water that is safe for dialysis, but, in some instances, the quantity of dissolved salts in the dialysate water may exceed maximum safety concentrations. Reverse osmosis membrane technology advanced greatly in the late 1970's with the development of thin film composite membranes which offered several advantages over celluloid acetate and polyamide membranes. The thin film composite membranes were more resilient to frequent cleaning and/or sanitization with stronger chemical agents.

The finished water quality is thus, higher in terms of total dissolved solid rejections.

When a reverse osmosis device is used as a pretreatment to deionization it serves primarily as an economic device to provide longer service life for the deionization system. Subsequent deionization of permeate (product) reverse osmosis water is usually unnecessary.

Microbiology of Hemodialysis Systems

The primary microbial contaminants of dialysis fluids are naturally-occurring water bacteria. These include gram-negative bacteria and non-tuberculous mycobacteria (see *Increased Risk of Clinical Infection* p. 24 above). These bacteria can survive and multiply in water containing little organic matter, such as deionization or reverse osmosis treated water. Disinfection strategies for HD systems are targeted at gram-negative bacteria. Although bacteria may be inactivated by exposure to chemical germicides, bacterial endotoxin may remain in the HD system. Endotoxins are produced by bacteria and can persist despite the absence of bacteria. Although non-tuberculous mycobacteria do not produce endotoxins, they are, compared to gram-negative bacteria, more resistant to chemical germicides and have been responsible for patient infections as a result of inadequately disinfected dialyzers.

AAMI Standards for Hemodialysis Water Quality

Water treatment is a vital aspect of HD in which knowledge and technical skills are of utmost importance. Each component of a water treatment system brings with it its own risks and requirements for safe and proper use as well as for monitoring and surveillance. A summary of the AAMI's recommendations (1993) for safe and proper water treatment and the use of water treatment system components is listed in Table 6.

Disinfection strategies for dialyzer reprocessing are quite different from those targeted to the water supply. While low-level disinfection is adequate for water treatment systems components, high-level disinfection is mandatory for dialyzer reprocessing. Water monitoring for reprocessing hemodialyzers therefore requires more stringent criteria. While there are no AAMI standards for endotoxin levels in water used to prepare dialysate, water for rinsing, reprocessing, and disinfecting dialyzers should contain less than 5 endotoxin units/mL (1 ng/mL).

The recognition that non-tuberculous mycobacteria can be resistant to certain germicides and still cause infection spurred the establishment of current safety microbiologic standards for dialyzer reprocessing. After reverse ultrafiltration and cleaning with bleach $< 1\%$; or hydrogen peroxide $\leq 3\%$ and peracetic acid $\leq 2\%$, manual or automated pressure tests for leaks should be performed. Dialyzers should then undergo disinfection/sterilization. Germicides are generally instilled into the blood and dialysate compartments and remain in contact for ≥ 24 hours. The 3 most commonly used agents are 4% formaldehyde, peracetic acid-hydrogen peroxide-acetic acid mixture (Renalin) and glutaraldehyde (Diacide). A 2% formaldehyde solution should not be used because some mycobacteria can survive in 2% formaldehyde at room temperature. However, even 1% solutions of formaldehyde may have excellent germicidal efficacy when dialyzers are incubated at 40° C for 24 hours.

Table 6. AAMI Hemodialysis Water Quality Standards*

Microbiologic and Endotoxin Standards for Dialysis Fluids

Type of Fluid	Microbial count (CFU/mL)[a]	Endotoxin (EU/mL)[b]
Water to prepare dialysate	≤ 200	No standard
Dialysate	≤ 2000	No standard
Water to rinse and reprocess dialyzers	≤ 200	≤ 5[c]
Water to prepare dialyzer disinfectant	< 200	≤ 5[c]

Chemical Contaminants Monitoring

Contaminant	*Suggested Maximum Level (mg/L)*
Calcium	2 (0.1 mEq/L)
Magnesium	4 (0.3 mEq/L)
Sodium	70 (3 mEq/L)
Potassium	8 (0.2 mEq/L)
Fluoride	0.2
Chlorine	0.5
Chloramines	0.1
Nitrates	2
Sulfate	100
Copper, Barium, Zinc	0.1 each
Aluminum	0.01
Arsenic, Lead, Silver	0.005 each
Cadmium	0.001
Chromium	0.014
Selenium	0.09
Mercury	0.002

*Association for the Advancement of Medical Instrumentation, American National Standards, Inc. AAMI Standard and Recommended Practices. Vol. 3: Dialysis 1993, Arlington, VA.
[a]CFU = colony-forming units; [b]EU = endotoxin units; [c]5 EU = 1 ng.

Hemodialysis Anticoagulation

For the majority of HD patients, systemic heparinization is usually used. Variations in heparin dosage for HD, which are common, cannot necessarily be judged by body weight. The patient should have heparin requirements assessed according to a series of whole blood activating clotting times (WBACTs) or whole blood activated partial thromboplastin time (WBAPTT) determinations; each HD unit must set up its own standards for WBACTs according to the reagent and system used. For

patients at high risk for bleeding, "tight" heparin, heparin-free dialysis, or citrate anticoagulation is used.

Systemic Heparinization

Heparin is administered either by the infusion pump method or by the bolus method. A bolus dose of heparin, usually 50 U/kg of lean body weight, is given and then an infusion pump is started, delivering approximately 500 – 1,000 U of heparin/hour. The loading dose is increased to 75 U/kg if the patient is receiving recombinant human erythropoietin (rHu-EPO). The infusion pump is usually stopped 30 – 60 minutes before the end of dialysis. The WBACT is monitored and aimed at about an 80 percent increase from baseline WBACT value during heparin administration. WBACT should be performed on each new admission and then once per month:

- before dialysis,
- 1 hour after initiation of dialysis, and
- half an hour before the end of dialysis.

Towards the end of dialysis, WBACTs in the range of 170 seconds are appropriate.

Patients with external shunts or cuffed catheters should have the WBACT kept at 3.5 to 4 minutes during dialysis.

Tight Heparinization

Indications for tight heparinization include moderate bleeding risks such as pericarditis or recent surgery. Target clotting times are 150 – 160 seconds with the WBACT method. To avoid fluctuations in heparin levels, the continuous infusion technique rather than the bolus method is recommended.

Dialysis Without Anticoagulation

This is the method used in patients with active bleeding or in whom heparin is contraindicated or in patients who are high risk for bleeding. This regimen uses initial rinsing of the extracorporeal circuit with saline and heparin, but without infusing this saline into the patient. After initiation of dialysis, periodic saline rinse with 300 mL every 15 minutes is needed. This technique is not recommended with subclavian or femoral catheters or patients in whom a blood flow of at least 300 mL per minute cannot be achieved. The risk of clotting of the dialyzer is about 15% with this regimen. Blood products or hyperalimentation lipids should not be administered during heparin-free dialysis.

Citrate Anticoagulation

Citrate anticoagulation is the method of choice for patients at high risk for bleeding or who are actively bleeding. In this technique, blood in the extracorporeal circuit is anticoagulated by chelating its calcium with sodium citrate and by using a zero-calcium dialysate bath. At the same time, an infusion of calcium chloride is given to the patient through the venous limb distal to the dialyzer. Approximately two-thirds of the citrate returns to the patient and is metabolized (approximately one-third of the citrate is dialyzed). Risk of clotting with citrate anticoagulation is low, and the advantage of this method over heparin-free dialysis is that high blood flows are not necessary. Serum calcium should be monitored and risk of alkalemia should be considered since citrate is also metabolized to bicarbonate. The citrate infusion rate is adjusted according to WBACT (measured in arterial line, downstream from citrate infusion, and aimed at 100% prolongation).

Regional Heparinization

In regional heparinization, protamine sulfate is used distal to the dialyzer to neutralize the heparin administered proximal to the dialyzer. A "heparin rebound" phenomenon may occur after regional heparinization from 2 – 4 hours after cessation of dialysis and persists for up to 10 hours, possibly causing hemorrhage. This technique is rarely used at present.

Alternative Methods of Anticoagulation for Hemodialysis

Heparin Coating of Hemophan

A method of priming the dialysis membrane with heparin before HD has been introduced and used successfully in high risk intensive care unit settings, as well as outpatients. This method is based on the idea that Hemophan dialysis membranes have a high affinity for binding heparin, and that the bound heparin exerts a localized antithrombotic effect without systemic anticoagulation [84]. Gretz [85 – 87] in Mannheim, Germany, compared Hemophan to polyacrylonitrile and polysulfone and reported less activation of coagulative pathways with Hemophan. A recent study by Mujais and Chimeh [84] performed sequential doses of heparin preloading consisting of 12,000 U, 16,000 U, and 20,000 U. Twelve patients were assigned in a random fashion to undergo 3 dialysis treatments with Hemophan dialyzers and preloading using the 3 different doses of heparin. It was determined that the optimal performance of this method requires the use of 20,000 U of heparin. They also compared the performance of the Hemophan dialysis with a 20,000 U prerinse to the use of saline flushing with cellulose acetate and polysulfone dialyzers. Minimal loss of clearance (at time 15 minutes and 3 hours of dialysis) was obtained with cellulose acetate and Hemophan (< 4%) and slightly larger loss of 6% was seen with the polysulfone dialyzer.

The method of heparin preloading was performed as follows. The arterial and venous ports were connected to a 1 L bag of 0.9% saline containing 20,000 U of heparin and the circuit is run at a 200 mL/min flow rate and 10 mL/min ultrafiltration rate for 20 minutes of recirculation time. At the end of the recirculation period, the pump is stopped, the arterial port is connected to a new 1 L bag of normal saline, and the circuit is flushed with 500 mL of saline with the effluent discarded. The lines are then connected to the patient, and dialysis is started in the usual fashion. This regimen is expected to allow for > 90% of the heparin dose to bind to the membrane. Unbound heparin is flushed out of the system by the heparin-free saline rinse.

Low Molecular Weight Heparin (LMWH) Anticoagulation

LMWH have recently been recommended as an alternative to unfractionated heparin for chronic HD patients [88 – 90]. Their most important advantage over unfractionated heparin is their prolonged half-life [91], enabling single bolus administration at the start of dialysis [89, 90]. Moreover, LMWH may have a more favorable hemorrhagic to antithrombotic profile than unfractionated heparin, since they interfere less with platelet aggregation [92, 93] and vascular permeability [94]. No bleeding complications occurred during a 12-month study in which 70 stable chronic HD patients were randomized to either unfractionated heparin or LMWH. With a target hemoglobin level of 6.5 g/dL, 19 patients on LMWH required transfusions of

76 packed RBC units, which was significantly less per dialysis/filtration session than 16 patients on unfractionated heparin, who required 88 units [95].

LMWH anticoagulation with nadroparin calcium [96] is performed as follows: nadroparin calcium [25,000 anti-factor Xa Institut Choay Units (anti-XaICU)/mL, Fraxiparine, Sanofi Winthrop, Maassluis, The Netherlands] is administered intravenously as a bolus at the start of dialysis session. The dose per kg dry body weight is adapted to the HCT and to the duration of the dialysis session:

Session ≤ 4 hours
HCT < 0.30: 150 anti-Xa ICU/kg = 60 IU/kg
HCT > 0.30: 200 anti-Xa ICU/kg = 80 IU/kg

Session > 4 hours
200 anti-Xa ICU/kg = 80 IU/kg

If the dialysis session lasts > 5 hours, 2/3 of the dose is given at the start of the session and 1/3 after 2.5 hours. The maximum dose to be given pending clot formation in the extracorporeal circuit is 350 anti-Xa ICU/kg.

Dialysate Composition

Dialysate Glucose

Contemporary dialysis fluids range from glucose-free to isoglycemia (5 – 5.5 mmol/L [90 – 100 mg/dL]) or slightly hyperglycemic (5.5 – 11.0 mol/L [100 – 200 mg/dL]). Most non-insulin dependent patients tolerate dialysis with glucose-free dialysate without ill-effects despite losing 25 – 30 g of glucose across the dialyzer. A few studies, however, have shown that this glucose loss may adversely affect intermediary metabolism of carbohydrates and proteins. The adverse effects of glucose-free dialysate include a reduction in plasma glucose, a corresponding decrease in plasma insulin levels, and a marked decrease in lactate and pyruvate levels. Although these biochemical measures often are sufficient to maintain serum glucose in the physiologic range, hypoglycemia may develop during the use of glucose-free dialysate, especially in the presence of cachexia, sepsis, diabetes mellitus, or drugs such as aspirin or propranolol. Available data at present also indicate that dialysate glucose does not play a significant role in determining total cholesterol levels in non-insulin dependent HD patients.

Dialysate Buffer

Bicarbonate dialysis is considered the dialytic treatment of choice in critically ill patients, conferring many benefits over acetate dialysis in these patients including a lower incidence of arterial hypotension, less hypoxemia, and improved left ventricular stroke volume. The mechanisms by which acetate buffer results in hemodynamic instability include direct vasodilation, stimulating the release of IL-1, a vasodilatory compound, and arterial hypoxemia which results from the transfer of CO_2 across the dialysis membrane, from blood to dialysate, with consequent reflex hypoventilation. Finally, acetate dialysate may have a myocardial depressant effect.Bicarbonate dialysis is the dialysate buffer of choice and confers advantages in critically ill patients. In chronic stable HD patients, patients who are unable to metabolize acetate well: elderly patients, patients with reduced muscle mass, malnourished patients and possibly, females, tolerate bicarbonate dialysate better. These patients may be par-

ticularly intolerant to acetate with the use of high-flux dialysis, because of the high influx of acetate with these dialyzers.

Dialysate Calcium

Because dialysate calcium equilibrates with the diffusable (ionized) fraction of calcium in the plasma, a dialysate calcium of 2.5 mEq/L is equivalent to serum calcium of 10 mg/dL. The use of a high dialysate calcium (3.5 mEq/L) or low dialysate calcium (≤ 2.5 mEq/L) entails separate advantages and risks. Numerous studies have shown a beneficial effect of high dialysate calcium on the indices of metabolic bone disease as well as a reduction in parathyroid hormone (PTH) levels. High-dialysate calcium has been shown to improve hemodynamic stability during dialysis by augmenting stroke volume and cardiac output. One of the complications of high dialysate calcium is the development of hypercalcemia with concurrent use of calcium-based phosphate binders and oral or intravenous 1,25 dihydroxy vitamin D_3. In a hemodynamically stable patient, and particularly those prone to hypercalcemia during treatment with vitamin D and calcium salts, a dialysate calcium concentration of 2.5 mEq/L is recommended.

Dialysate Potassium

Low dialysate potassium can precipitate ventricular ectopy. This is most pronounced in patients with left ventricular hypertrophy, impaired left ventricular function, or in patients taking digoxin. Therefore, for patients at risk for dysrhythmias, the use of dialysate potassium < 2 mEq/L should be avoided.

Dialysate Sodium and Variation Programs

With the refinement of HD technology, variable sodium profiles during dialysis are now possible. Three different profiles have been described (as depicted in Figure 1, chapter on "Complications During Hemodialysis").

A recent study compared steady dialysate sodium of 140 mEq/L to linear sodium ramping (155 to 140 mEq/L) or stepwise ramping (sodium 155 mEq/L for 3 hours and 140 mEq/L for 1 hour) [97]. There was no major difference between the 2 ramping protocols, but compared with standard dialysis, both decreased total number of hypotensive episodes as well as that of cramping during dialysis. Between dialysis treatments, however, patients complained of more fatigue and thirst. Interdialytic weight gain following ramping was 5.1% of body weight (compared to 4.4% without ramping). Blood pressure also increased following ramping, from 143/79 mmHg to 152/81 mmHg. Even though this study indicates that most patients will have more problems between dialysis sessions when ramped, some patients (22%) do derive great benefits, with a dramatic decrease in hypotension and cramps, which will be worth the tradeoff for postdialysis complications. Interestingly, in another study comparing dialysate sodium to 140 mEq/L to a programmed exponential decrease of dialysate sodium from 155 mEq/L to 135 mEq/L which was held constant for the final half hour of dialysis, 63% of the treated hypertensive subjects were able to stop or reduce their medications on the variable-sodium program [98]. Other investigators, however, have not found any hemodynamic advantage for sodium-gradient compared to a fixed high-sodium dialysate of 140 – 145 mEq/L. In these patients, sodium-

gradient dialysis may offer its greatest benefits in 2 clinical situations:

– the initial dialysis session for a patient with advanced renal insufficiency and an extremely elevated urea concentration (> 200 mg/dL), in which case sodium modeling might decrease the risk of dialysis disequilibrium syndrome; and

– patients with a low urea mass transfer coefficient, who exhibit a delay in equilibration between intracellular and extracellular fluid compartments. In these patients, sodium-gradient dialysis may allow for more balanced urea and volume transfer.

Summary

Transport and biocompatibility characteristics are 2 important considerations when choosing HD membranes. Because of concerns about middle molecule transport and biocompatibility, the original cellophane membrane has been gradually replaced by modified cellulosic membrane and synthetic membranes for clinical use. Because of large economic benefits, dialyzer re-use has become an integral part of chronic HD in the U.S. and in some European countries. When the recommended practice guidelines by the AAMI are carefully followed, dialyzer re-use is relatively safe. The development of disinfectant methods using heat or heat and 1.5% citric acid is a promising for polysulfone membranes. Finally, the life-sustaining aspects of HD with its dramatic reversal of uremic toxicity should not obscure the fact that HD is, at best, an approximation of natural kidney function and improper clinical application of HD technology can severely compromise its therapeutic adequacy.

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Peritoneal Dialysis

Ploumis S. Pasadakis and Dimitrios G. Oreopoulos

Introduction

Although several attempts were made to use the peritoneal cavity for dialysis in the late nineteenth century, its use in the management of patients in end-stage renal disease (ESRD) was accepted as a long-term therapy only after Tenckhoff's development of the indwelling silicon-rubber catheter (1963) and the introduction of continuous ambulatory peritoneal dialysis (CAPD) in 1976.

The concept of CAPD was based on mathematical calculations of the peritoneal-membrane kinetics and the requirements to achieve adequate removal of uremic waste products to sustain life. Popovich et al. suggested a scheme of five 2 L exchanges daily, 7 days a week to achieve an adequate control [1]. The main advantages of the new technique were good steady-state biochemical control, more liberal dietary and fluid intakes than with hemodialysis, improvement of anemia and increased well-being of patients, who were able to undertake more physical and social activities away from the hospital.

The need to disconnect the peritoneal catheter from peritoneal dialysis (PD) system to perform each new exchange remains the major source of contamination and of subsequent peritonitis. Several devices have been developed to minimize the risk of contamination, and many attempts have been made to enhance the efficiency of PD by increasing fluid flow, exchange volume, and by optimizing dwell time.

The first continuous cyclic peritoneal dialysis (CCPD), which retains the physiological advantages of CAPD while eliminating daytime exchanges, used a dialysis cycler with a timer; it allowed a programmed delivery of three or more 2 L nocturnal exchanges while a fourth exchange was left to dwell throughout the day [2]. This system, which provides a convenient, continuous therapy and a higher dose of dialysis, has caused a recent resurgence of interest in automated PD. Combinations of CAPD and CCPD have recently been utilized, particularly in large patients with no residual renal function.

Most countries now offer PD in their chronic dialysis programs and many patients have chronic support by this modality in their end stage renal failure. According to the recently reported data of United States Renal Data System (USRDS), CAPD/CCPD modalities accounted for 14.7% of dialysis therapies [3].

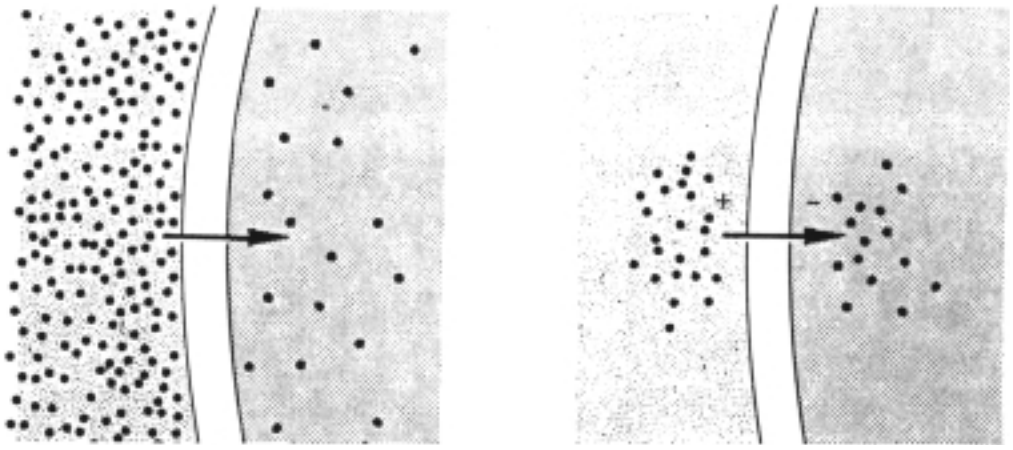

Figure 1. The semipermeable peritoneal membrane. Small solutes are moving through pores by the effect of concenration (left) and electrical (right) difference.

The Physiology of PD

Solutes that accumulate in the blood of patients with ESRD such as urea, creatinine, phosphate, potassium and hydrogen diffuse through the peritoneal membrane into the dialysis solution that has been infused into the peritoneal cavity. Addition of lactate to the solution helps to correct the acidosis when it diffuses into the circulation and is changed by hepatic metabolism to bicarbonate.

Dialysis represents an exchange between the blood in the interstitial capillaries of the peritoneum (blood compartment) and the infused solution (solution compartment) across the peritoneal membrane. The latter, acting as a semipermeable membrane, allows water and small molecules to pass through faster than larger molecules. The driving force by which the various solutes move from the higher (blood and body tissues) to lower concentration compartment (dialysis solution) is the concentration gradient of solutes between plasma and dialysis solution (Figure 1.). In the same way, the driving force for water transport is the pressure gradient generated from differences in hydrostatic, osmotic and oncotic pressures across the peritoneal membrane. A crystalloid osmotic pressure gradient is achieved by the addition of glucose (dextrose) in various concentrations to the solution while colloid osmosis can be induced by adding large molecules such as glucose polymers (icodextrin).

In addition to the phenomena of diffusion and ultrafiltration, there is also considerable absorption from the peritoneal cavity. Such absorption occurs during the equilibrium period either directly into the peritoneal capillary microcirculation or via peritoneal lymphatics.

Peritoneal Circulation-lymphatics

The peritoneal cavity is lined by a continuous serous membrane consisting of a layer of squamous mesothelial cells resting on a thin submesothelial basement membrane and the peritoneal interstitium. Venous flow from the parietal peritoneum drains into the inferior vena cava and systematic circulation while venous drainage from visceral peritoneum

flows into the portal system. This is important because, during their first circulatory pass, intraperitoneally administered drugs will be handled partly by the liver.

Approximately 25% of the cardiac output is directed to the splanchnic vascular bed and the subsequent abdominal splanchnic blood flow usually exceeds 1200 mL/min at rest; however, gas diffusion techniques have shown that the "effective peritoneal capillary blood flow" available for PD is approximately 68 – 82 mL/min.

Lymph drains from the peritoneal cavity mainly through specialized lymph stomata located in the subdiaphragmatic peritoneum; these passages open and close with inspiratory and expiratory diaphragmatic movements. From the diaphragm and through the subdiaphragmatic lymph nodes, almost 80% of the lymph drain to the venous circulation via the right lymph duct. Thus lymphatics draining returns excess intraperitoneal fluid and protein from the peritoneal cavity to the systematic circulation while they provide the only pathways for absorption of intraperitoneal biologically inert particles, colloids and cells.

Solute and Water Transport Across the Peritoneum

The principal determinants of the rate of diffusive solute transport for PD are the concentration gradient between blood and dialysate ($C_p - C_d$), the molecular weight of the solute, and the peritoneal membrane resistance. By changing the peritoneal solution as frequently as possible, we can keep the concentration gradient > 0 and thus maintain a continuous solute removal (Figure 2). However peritoneal clearances of urea cannot exceed a maximum of 40 mL/min even with the more rapid exchanges of dialysate, which

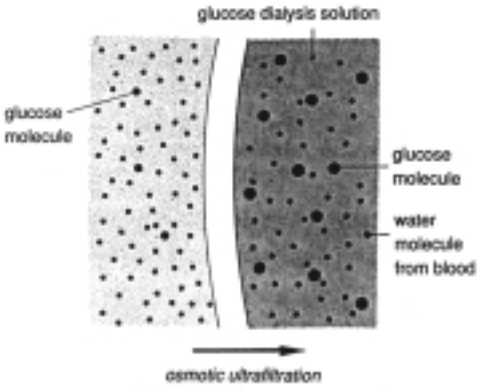

Figure 2. Osmotic ultrafiltration across the peritoneal membrane. Glucose molecules in the dialysis solution generate the driving force for water removal from the peritoneal capillaries to peritoneal cavity.

achieve a flow rate of 4 – 6 L/hour (Figure 3) [4]. Regarding molecular size, smaller molecules diffuse more rapidly than larger ones and the peritoneal membrane does not impede the passage of solutes up to the size of inulin (5200 daltons). On the contrary the transport of larger solutes such as β2-microglobulin (β_2M), myoglobin and albumin, appears to be clearly restricted. Such large substances create oncotic pressure across the membrane, which acts in the same way as hydrostatic pressure, causing bulk flow of water through the pores. During this convective flow, the concentration of solutes, such as sodium and potassium, per L ultrafiltrate usually is far below their respective concentrations in the extracellular fluid, because of the sieving effect of the peritoneal membrane.

Ultrafiltration in PD

The presence of glucose in the peritoneal solution generates an osmotic pressure that induces osmotic ultrafiltration, the main mechanism whereby fluid is drawn from blood into the dialysate. This bulk movement

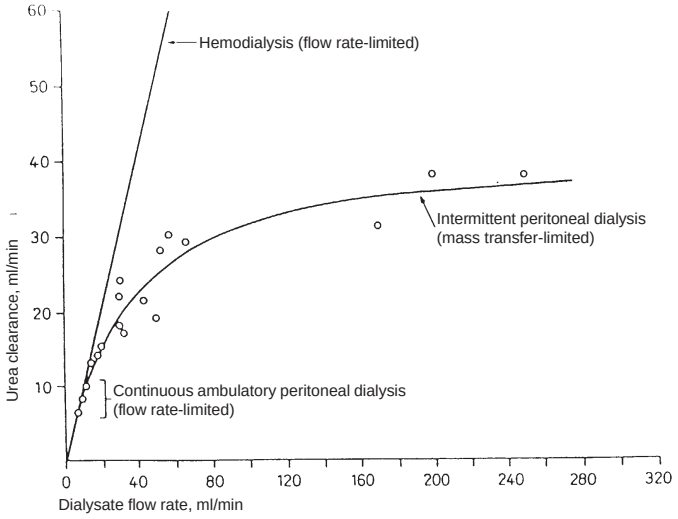

Figure 3. Clearance of small solutes (urea clearance) as a function of dialysate flow rate in HD and PD treatment.

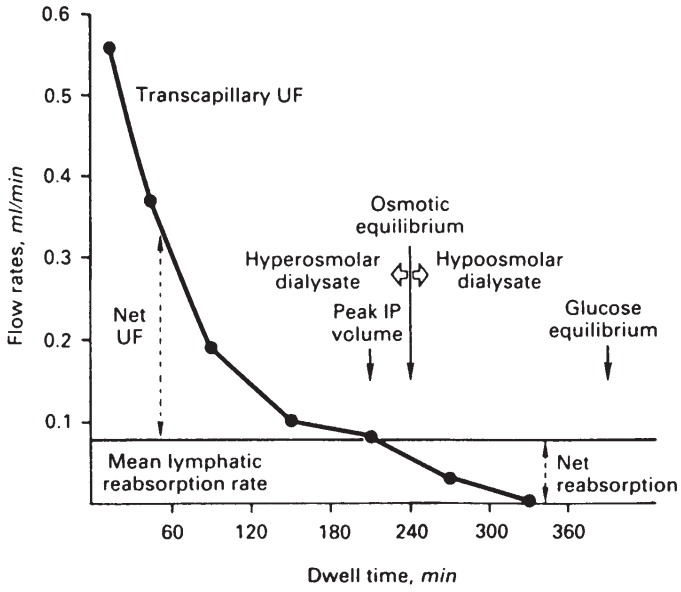

Figure 4. Effect of dwell time on mean transcapillary ultrafiltration. The peak intraperitoneal volume occurs when transcapillary ultrafiltration rate equals the lymphatic absorption rate.

is responsible for a substantial percentage of solute removal (convective transport), which is increased (up to 20% of total removal) for substances with a large molecular weight.

Net ultrafiltration rate, a balance between osmotic ultrafiltration removing water and solutes into peritoneal cavity and lymphatic absorption from the peritoneal fluid, is maximal at the beginning of an exchange when the glucose concentration is at its maximum. Then there is an exponential decrease because of a decline in the glucose concentration gradient due to glucose absorption and dilution by ultrafiltrate, and of lymphatic absorption of peritoneal fluid at a rate of about 0.5 to 1.5 mL/min (Figure 4). Peak intraperitoneal vol-

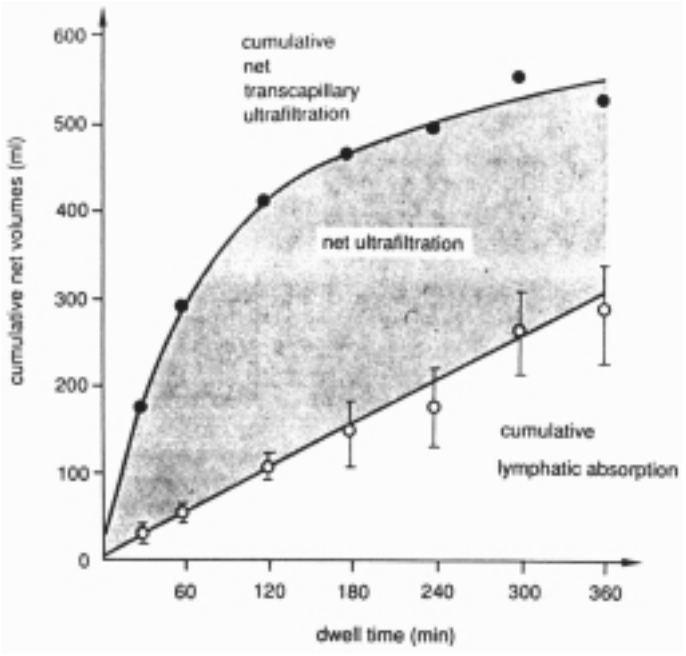

Figure 5. Cumulative net ultrafiltration during PD exchange.

ume occurs at about 120 – 180 min of dwell when ultrafiltration rate equals absorption rate (Figure 5). The maximal transcapillary ultrafiltration induced by 3.86% glucose dialysis solution in the supine position averages 15 mL/min.

standing the peritoneal transport characteristics during the various forms of PD help the operator to choose the most efficient form for the individual patient. Also knowledge of peritoneal membrane characteristics is important to adequate dialysis and to the manipulation and management of some of the common clinical difficulties during PD.

Assessing Peritoneal Ultrafiltration and Solute Transport

The total volume of water and solutes removal from the body during an exchange depends on the degree of equilibrium established during the dwell period, across the peritoneal membrane, between the peritoneal capillary blood and the infused solution. Under-

Clinical Evaluation of Peritoneal Ultrafiltration and Solute Transport – Peritoneal Equilibration Test (PET)

Of the several methods developed for the assessment of peritoneal membrane function, the most commonly used is the PET (Table 1). The reproducibility of this test was demonstrated in systematic studies of CAPD patients, which showed differences in water and solute removal rates during 4 hours dwell time

Table 1. Peritoneal Equilibration Test

1. Pretest exchange fluid is drained completely over 20 min in the sitting position, after an overnight exchange dwell for 8 – 12 hours.

2. A warmed 2 L of 2.5% glucose dialysis solution is weighted (V1) and infused at a rate 200 mL/min;the patient should roll from side to side for better solution mixing after each 400 mL infusion.

3. At the completion of infusion (time 0), 200 mL of peritoneal fluid is drained into the bag, mixed well, a 10 mL sample is taken (S0) and the remaining 190 mL is reinfused

4. The patient is ambulatory during dwell time.

5. After 2 hours dwell*, another dialysate sample (S2) and a blood sample are taken.

6. After 4 hours dwell, the dialysis solution is drained out completely in sitting position, the bag with dialysate is again weighted (V2) and a new sample is taken (S4). Assuming a specific gravity of 1.0, ultrafiltrate is measured by the subtraction V2 – V1.

7. Concentration of creatinine and glucose are measured in solution and blood samples+.

8. Measurement of a) dialysate to plasma ratios (D/P) of creatinine in the samples S2,S4 and b) the ratio D/D0 of the solution glucose concentrations (D) in S2,S4 and the concentration at the beginning (S0).

* Time is measured from the end of infusion
** Because glucose interferes with the Jaffe reagent for creatinine, to avoid overestimation of the creatinine in the dialysis bag, a correction factor must be multiplied.

in 2 L exchange using 2.5% glucose [5]. The differences are graphically presented in equilibration curves. Using this test, the patients were classified into groups according to dialysate to plasma ratios (D/P) of solutes, and glucose absorption (Figure 6):

– The mean D/P values for a 4-hour, 2.5% glucose exchange is 0.65 for creatinine; lower values, i.e. < 0.50, characterize patients who have low permeability transport properties.
– Glucose absorption is more rapid early in the dwell and in patients with high peritoneal permeability, this produces a severe decrease in the osmotic gradient that is responsible for ultrafiltration. Thus, after a 4-hour 2.5% glucose exchange, such patients have lower drainage fluid glucose levels (< 500 mg/dL compared to normal levels of 720 mg/dl).

Using these results, patients can be divided into 4 groups:

– Low transporters who show: a) low D/P of creatinine (< 0.50), and b) low rate of glucose absorption inducing peak ultrafiltration late in the exchange.
– High transporters who show: a) high D/P of small solutes and peritoneal clearances that are close to unity in 4-hour exchange, and b) rapid absorption of glucose inducing peak ultrafiltration early in an exchange. Ultrafiltrates volumes are minimal in 4-hour exchange due to fluid absorption.
– Low average and high average transporters who present with intermediate equilibration rates.

A recent PET study found that these groups, were distributed between CAPD patients as follows: high average (53.1%), low average (30.9%), high (10.4%) and low (5.6%) [6].

In a 4-hr exchange of 2 L (2050 mL) of 2.5% glucose, the net ultrafiltrate is approximately 320 mL (2370 mL drainage volume-2050 mL instilled volume). Because net ultrafiltration rate is a balance between osmotic ultrafiltration removing water into peritoneal cavity and the lymphatic absorption of peritoneal fluid, a decrease in ultrafiltrate represents either a decrease in osmotic ultrafiltration or an increase in lymphatic absorption.

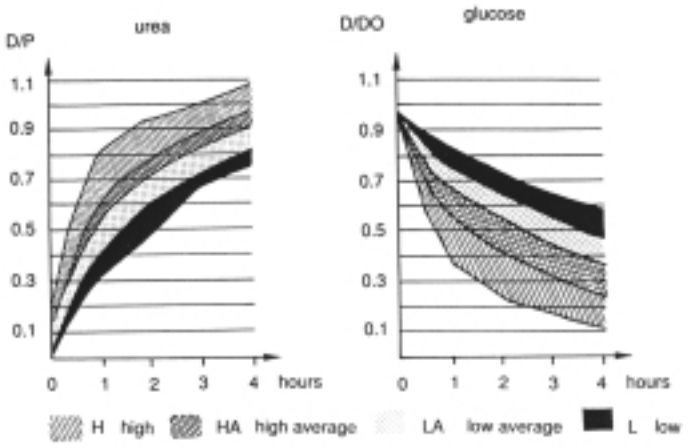

Figure 6. The equilibration test for urea and glucose absorption. Area shaded in different patterns portray results representing high (H), high average (HA), low average (LA) and low (L) peritoneal equilibration rates, in patients on CAPD.

In assessing baseline peritoneal membrane permeability, one must make PET measurements 3 – 4 weeks after the initiation of PD. The results should not be used as a precise measure of dialysis adequacy, but rather as a general guide to the prescription of the more suitable mode of dialysis for the patient's peritoneal membrane characteristics. In general, average transporters do better on continuous PD schedules (long dwell) while high transporters do better on intermittent dialysis (short dwell). The standard continuous and intermittent PD regimens include:

– CAPD with the continuous presence of dialysate in the peritoneal cavity, drained and reinstilled 4 – 5 times/24 hours,
– CCPD which uses a dialysis machine with a timer to provide a programmed replacement of dialysate in 3 to 5 two liter (2 L) nocturnal exchanges; in the morning, the patient disconnects the cycler and leaves a fresh 2 L solution to dwell throughout the day, and
– nocturnal intermittent peritoneal dialysis (NIPD, dry PD) that is similar to CCPD but differs in that the abdomen is left empty during the daytime, while the nocturnal exchanges are increased to 5 – 8 exchanges.

Peritoneal Solute Clearances (K_p)

K_p expresses the volume of plasma cleared of the solute by the peritoneal membrane per unit time. This can be measured using the equation

$$K_p = (V_t / t) \times (D/P)$$

where V_t is the volume of dialysate drained at the end of the exchange, t is the duration of the exchange and D/P is the dialysate-to-plasma ratio for solute concentrations in that exchange. By changing the equation to

$$K_p \times t = V_t \times (D/P),$$

it can be shown that the clearance-time product (solute removal) is equal to the volume of dialysate drained times the D/P ratio.

In patients with low peritoneal transport rates, the equilibration of solutes (D/P) and therefore the peritoneal clearance per exchange increase almost linearly during the exchange and consequently long-dwell exchanges are critical for solute removal. On the contrary, in high transporters the rapid increase in D/P allows one to perform short-dwell exchanges to maintain better ultrafiltration rates.

In CAPD the product ($K_p \times t$) can be calculated for a 24-hour period by pooling the drained volumes of all exchanges (V_d) during that period, measuring the D/P and multiplying the $V_d \times$ (D/P). Similar calculations are performed for a patient on NIPD, in whom the V_d represents the total drained volume of all nightly exchanges. The serum samples can be obtained from CAPD patients at any time, while in CCPD patients, they are taken at the midpoint of the long daily dwell. In NIPD an average of pre- and postdialysis concentrations may be more suitable because the plasma solute concentration (P) may change over the session.

Table 2. Composition of PD Solutions

	Commercial Solution	Usual plasma level in dialysis patient
Sodium (mmol/L)	132 – 134	135 – 142
Potassium (mmol/L)	0 – 2	4 – 6
Calcium (mmol/L)	1.25 – 1.75	1.15 – 1.29
Magnesium (mmol/L)	0.25 – 0.75	0.65 – 0.70
Chloride (mmol/L)	95 – 106	95 – 100
Lactate (mmol/L)	35 – 40	1 – 2
Glucose (gr/dL)	1.5 – 4.25	70 – 120
pH	5.5	7.2

PD Apparatus and Devices

Dialysis Solutions

Dialysis solutions for CAPD are available in sterilized collapsible plastic containers in several volumes and various concentrations of the osmotic agent glucose. Solutions with 1.5, 2.5, 3.5, or 4.25% dextrose contain 1.36, 2.27, 3.17 and 3.86 gr. of D-monohydrate glucose, respectively. The listed and the true glucose concentrations differ because the molecular weight of D-glucose monohydrate is 10% greater than that of anhydrous glucose. The clear underfilled plastic bags contain 0.25, 0.5, 0.75, 1.0, 2.0, 2.5 and 3.0 L; the potential volume of the container exceeds by about 50% the volume of the contents to accommodate any ultrafiltrate. There are also 5.0 L plastic containers for cycling machines.

The composition of PD solution is tailored to correct the electrolyte and acid-base imbalances by restoring the normal composition of the body fluids (Table 2).

Electrolyte Homeostasis

In the uremic syndrome the accumulated sodium, potassium and magnesium ions have to be removed and the associated hypocalcemia and acidosis have to be corrected. Depending on the concentration gradients, PD removes only small amounts of sodium and chloride while it removes large amounts of potassium and magnesium.

Because of the peritoneal membrane's sieving effect, the net removal of sodium per L ultrafiltrate (70 mmol/L) is significantly lower than the plasma sodium concentration. This hyponatremic ultrafiltrate further dilutes the dialysate and with short dwell exchanges, the greater removal of water tends to produce hypernatremia. Clinical studies have reported no specific side effects with the use of standard CAPD solutions of 132 – 134 mmol/L of sodium, while the use of lower sodium concentrations can accelerated the diffusive loss of sodium. Variations in the net daily removal of sodium can be attributed to differences in dietary intake, in residual renal function or to

intrinsic autoregulatory mechanisms for the adjustment of removal rates [7]. Experimentally, various sodium concentrations have been used, as higher sodium concentrations (137 mmol/L) to correct orthostatic hypotension, and ultra low sodium (98 mmol/L) to avoid fluid overload in patients with insufficient ultrafiltration.

Potassium should equilibrate slightly faster than sodium because of its lower nuclear charge and its smaller hydration radius; with four 2 L exchanges per day about 30 mmol of potassium are removed with dialysate. Because this value is lower than the usual daily intake (70 – 80 mmol), enhanced intestinal potassium excretion is essential to maintain normal serum potassium values. The hypokalemia found in 10 – 36% of CAPD patients had been attributed to their anabolic state, malnutrition and the use of large doses of diuretics [8].

Although minor changes in serum magnesium are difficult to interpret, hypermagnesemia is common in dialysis patients. By lowering magnesium in the dialysis solution, one can treat hyperphosphatemia with magnesium salts as an additional aluminum-free phosphate binder [9].

Since standard CAPD solutions contain 1.75 mmol of calcium – a concentration that is higher than normal serum diffusible calcium levels (1.15 – 1.29 mmol) calcium is absorbed from the dialysate when such solutions are used. Convective transport counteracts diffusive uptake and during dialysis with a 4.25% glucose solution, ultrafiltration may cause a decrease in total calcium uptake. Despite the otherwise favorable effect of calcium absorption because of uremic hypocalcemia, in the presence of normal serum calcium levels, this absorption may be associated with hypercalcemia and soft-tissue calcification when using calcium-containing phosphate binders. To avoid such side effect, low calcium solutions have been introduced. A major risk of these new solutions is the progression of hyperparathyroidism, which may be enhanced in patients undergoing two or more 4.25% exchanges per day. Such patients require a frequent monitoring of calcium and PTH levels.

Acid-base Balance

Two of the major achievements of PD are the correction of metabolic acidosis and the maintenance of satisfactory acid-base status. Standard solutions contain lactate (L- or D-racemic forms) as a bicarbonate-generating agent because of the technical difficulties in preparing, sterilizing and storing solutions containing mixtures of bicarbonate, calcium, magnesium and glucose. The absorption of lactate is maximal during the first few minutes of dwell, which permits an adequate buffer transfer even with rapid exchanges, while long dwell exchanges enable an almost complete buffer transfer independent of the initial lactate concentration. During dwell, bicarbonate diffuses back into the dialysate at a rate determined by blood bicarbonate concentration, while ultrafiltration enhances this loss. Organic anions, which play the role of effective alkaline equivalents also are drawn into the dialysate.

Although lactate is a powerful peripheral vasodilator that also effects myocardial contractility, there is no clear evidence that these actions have clinical relevance during dialysis with a lactate buffer. Patients with hepatic disease may have a lower metabolic rate with a consequent increase in serum lactate levels.

Generally the low pH of dialysis solution (≈ 5.5) is well tolerated, however, during inflow some patients may complain of pain, which may be relieved by neutralizing the solution pH with alkali before instillation.

Other Osmotic Agents

Several low-molecular-weight agents – glycerol, sorbitol, xylitol, fructose and amino acids have been used to generate a high osmotic gradient in peritoneal transport, but glucose appears to be the safest, most effective and most easily metabolized agent for this purpose. Amino acid solutions have been introduced to achieve the dual goals of glucose substitution and nutritional improvement of malnourished CAPD patients [10]. Despite their significance in nutritional efficacy, one must consider associated increases in blood urea nitrogen (BUN) levels, the tendency to metabolic acidosis and increased cost.

Larger molecules of less absorbable substances – (glucose polymers, gelatin, dextrans, polycations, and polypeptides) have been studied, in an attempt to slow the dissipation of the osmotic gradient and, at the same time, to reduce the calorie load. Recently Krediet et al. have shown that icodextrin, a glucose polymer consisting mainly of α-1,4 linkages between glucose molecules, is superior to glucose in the induction of net ultrafiltration during long dwells – a feature that may be important during peritonitis episodes and in patients with ultrafiltration failure [11].

Peritoneal Catheters

For acute PD the rigid peritoneal catheter provides a quick, easily accessible route into the intraperitoneal cavity at the bedside. Once inserted, it can be used safely for a maximum of 72 hours beyond which there is an increasing risk of peritonitis. Thus when one anticipates that the patient will need PD for more than one week, a permanent catheter should be installed. Furthermore their use is accompanied by a high rate of complications.

The permanent catheter has a number of advantages:

- safe implantation without major surgery,
- adequate dialysate inflow and outflow, and
- maintenance of its position for long periods without intra-abdominal migrations.

The most widely used device for chronic PD is the Tenckhoff catheter and its modifications, all of them being straight or slightly curved with several side holes at their intra-abdominal part. They are made of silicon rubber or polyurethane with one or two cuffs of Dacron velour. Profuse collagen tissue ingrowth between the fibers provides a strong bond with the surrounding tissues. This fibrous tissue fixes the cuff in position and prevents the passage of bacteria into the subcutaneous channel. Experienced surgeons or nephrologists should implant these catheters in the operating room or at the bedside, using a guidewire and dilators, or peritoneoscopy.

"Connectology": Transfer Sets and Dialysis Systems

The dialysis solution is infused into the peritoneal cavity via a plastic tubing transfer set that connects the plastic bag and the peritoneal catheter. Commonly the transfer set is connected to the catheter via an on-line plastic connector, which screws onto a special titanium Luer-Lock connector. The other end is connected to the solution bag; this is an important connection because approximately two-thirds of all episodes of peritonitis can be attributed to touch contamination of this connection [12]. Many connection systems have been developed to avoid touch contamination; these are based on individual exchange procedures – manual, mechanical, sterilized, anti-

septic, and disposable. The term "connectology" refers to these different equipment and methods of connections.

A straight or Y-shaped transfer set is connected to the solution bag via connection techniques that can be categorized as one of 3 types:

– the spike and port method,
– the Luer-lock method, or
– the mechanical assist.

The standard spike and port connection is the simplest of these; one pushes a plastic spike at one end of the transfer set into a small rubber port on the dialysate bag. A connection shield that contains a sponge soaked with povidone-iodine gives added protection at the spike-outlet port site. The sponge, which remains in place during the dwell period, is removed at the time of the next exchange.

The halves of the Luer-lock connectors are closed with a twisting action that seems to be easier to perform and prevents touch contamination without the need for fine hand control. The Luer system comes with a protective, povidone-iodine clamshell or a cap containing antiseptic.

The mechanical assist devices designed to reduce peritonitis are portable, convenient and easy to use. In most of them, a lever-assisted exchange system helps patients, particularly those with visual and manual impairment, to insert the transfer set spike into the port of the dialysis bag. Some of these devices also include a system that sterilizes the connection site before the infusion. The ultraviolet (UV) light device (UV-Flash) has a mechanical system to assist the patients in spiking the transfer set, and an UV light system that irradiates and sterilizes the spike and port before connection.

In the simplest dialysis system fresh dialysis fluid is infused from a bag that, once empty, is rolled up and stored in a little pouch on the patient's body, keeping the tubing clamp closed. At the end of the dwell, the bag is unrolled and placed on the floor, the clamp is opened and the effluent is drained into the bag. Then the spike of the transfer set is removed from the used bag and inserted into a new one. This transfer set is changed once every 6 months by a dialysis nurse. This system, though inexpensive, is used only infrequently because newer systems provide a lower peritonitis rate.

The Y-shaped transfer sets consisting of a stem and two limbs, one for infusion of the dialysis solution and the other for its drainage. The concept behind the Y systems is that before connection with the bag, the patient runs a small volume of fresh dialysate (30 – 100 mL) into the drain bag (flush), which carries with it any contaminating bacteria. Similarly after connection with the catheter, the patient drains out fluid from the abdomen before he infuses fresh dialysate, thus washing out any contaminating bacteria (flush after connect). With its "flush before fill" procedure, the Y set gives significantly lower peritonitis rates than straight sets; also, because of the disconnection there is less mechanical stress on the exit site and tunnel and hence fewer episodes of minor trauma and consequently of exit-site infection.

Some Y-sets come attached to an empty sterile drain bag, which the patient connects to his catheter and to the appropriate fresh dialysis bag. To minimize the connections (to the peritoneal catheter), sterile sets are available which include the empty and the full dialysate bag (twin or double bag systems). At the end of the exchange, the bags, the lines and the transfer set are disconnected and disposed. Also reuseable Y-sets are available which combine the flush-before-fill advantages with a disinfectant that is injected into the Y-set lumen immediately after an exchange. This system, called O-set, because of the O shape

Table 3. Characteristics of the Main Regimens of PD

Feature	CAPD	CCPD	NIPD
Number of exchanges /week	28	28	49 – 56
Daytime exchanges /week	21	7	0
Daytime dwell (hour/week)	84	98 – 112	0
Nocturnal exchanges/week	7	21	49 – 56
Nocturnal dwell (hour/week)	56 – 70	45 – 60	28 – 42
Dialysis time (hours/week)	168	168	56 – 70
Cycler time (hours/week)	0	56	56 – 70
Dialysate volume (L/week)	56	56	98 – 112
Number of "connections"/week	28	14	7
Peritoneal Clearances C_{Cr} (L/week)			
Urea / creatinine	57/47	57/47	62/39
Ultrafiltration L/D	1.3 – 2.0	0.7 – 1.7	1.5 – 2.0

formed by the two joined limbs. At the time of the next exchange, the antiseptic is drained out and the dialysate effluent rinses the stem. O-Sets have not gained wide acceptance because of the frequent, accidental instillation of antiseptic into the peritoneal cavity.

PD Machines

These machines deliver predetermined volumes of solution into the peritoneal cavity, and drain it out after a programmed dwell time. A heater warms the solution to body temperature, and the force of gravity directs the fluid through lines that are clamped (on or off) to permit flow in or out of the peritoneal cavity. Dialysis solutions of different glucose concentrations can be attached simultaneously usually with the spike-and-port method into a multipronged manifold, which can hold several dialysis containers (up to 5 – 8 containers of 3 – 5 L each), provide an efficient solution volume for nightly exchanges. Because the machine always controls the inflow volume, it is not essential to have an accurate volume in each container.

Technique of PD – Choice of Treatment Modality

Prescription of a PD technique includes:

- the method of dialysis – manual or automated,
- the regimen – intermittent or continuous,
- the infusion volumes and the type of solutions to be used per exchange, and
- the volume of solution to be infused over a specified time period – dose of dialysis.

Table 3 shows some characteristics of the main regimens.

Intermittent Regimens

These regimens are especially suitable for patients who maintain some residual renal function and/or high peritoneal transport rates. There are 3 schedules:

Intermittent Peritoneal Dialysis (IPD)

Here, a 16 – 20 hour treatment is given 2 – 3 times a week, using a cycler machine. The usual dose is about 40 – 60 L per session (80 – 120 L/week). This regimen is most suitable for high and high-average transporters who maintain renal residual function.

Nocturnal Intermittent Peritoneal Dialysis (NIPD)

Treatment is given every night while the patient sleeps using a cycler to perform 7 – 8 exchanges over 8 – 10 hours. The daytime is free of exchanges. The usual volume per session is 14 – 16 L (98 – 112 L/week). This method is particularly useful in high transporters who have a decreased ultrafiltration with 4 – 6 hours dwell; in these patients this method gives a clearance of small solutes equivalent to that of CAPD. Also NIPD is helpful to patients with hernias, pericatheter leaks and back pain because it operates at a lower intraperitoneal pressure because the patient is supine during dialysis. The alleged increase of peritoneal fluid leukocyte and higher gamma globulin concentration during the long dwell time may contribute to the lower incidence of peritonitis in these patients. The major disadvantage of this technique is its reduced removal of solutes, particularly the larger molecules. Daytime IPD may be useful as a hospital-based therapy in bedridden, severely handicapped patients, who cannot sustain hemodialysis.

Daytime Ambulatory Peritoneal Dialysis (DAPD)

DAPD is treatment for 12 – 16 hours is given only during the day when the patient is ambulatory, in several short exchanges with 3 – 4 hours dwell time. The short time of equilibrium in this modality can be used only by patients who maintain residual renal function and/or high peritoneal transport rates – characteristics that allow small solutes to reach their peak clearances and the ultrafiltration volume to balance the intake of fluids. The dose per session is 8 L (56 L/week).

Continuous Regimens

The standard CAPD and CCPD usually provide adequate dialysis in patients with average peritoneal transport rates.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

This – the most common prescribed dialysis throughout the world – uses three or four 2L daytime exchanges during the day and another before bedtime; dialysis solution is continuously present in the abdomen. This continuity provides a more “physiological” steady state and confers some advantages in body fluid control, in control of hypertension, while it is easier to achieve normal blood sugar levels in diabetics with the intraperitoneal administration of insulin in each exchange.

The volumes and the glucose concentration of the solutions are selected according to pa-

tient's needs and peritoneal transport characteristics. Usually the overnight exchange with 8 – 10 hours dwell time is of 2.25%, or in the presence of low ultrafiltration, a 4.25% solution is used to maintain the osmotic gradient and avoid fluid absorption. The standard daily dose of 8 L (56 L/week) can be increased by increasing the volumes per exchange (to 2.5 or 3.0 L/exchange), or by increasing the number of exchanges (5 exchanges/day).

As a treatment CAPD is suitable for patients with average, low or high peritoneal transport rates.

Continuous Cyclic Peritoneal Dialysis (CCPD)

This technique retains the physiological advantages of CAPD but eliminates diurnal exchanges; using a dialysis cycler, three 2 L exchanges are given at night, while a fourth 2 L exchange is left to dwell throughout the day over 14 – 16 hours. This method provides the same dose as CAPD and is more suitable for patients who need a partner to help them with the dialysis. Also this method is attractive for active individuals who otherwise would be inconvenienced by the daily interruptions required by CAPD. The lower incidence of hernias and pericatheter leaks associated with this modality may be due to reduced mean intraperitoneal pressure during the hours of activity. The dose can be increased by increasing the nightly treatment time (8 – 10 hours), the volume of each exchange, or by performing more daily exchanges.

Alternate PD Regimens

The standard regimens can be modified to provide adequate dose of PD, particularly in anuric patients, or in those with large body size and low or even low-average transport kinetics. When needed, performing 2 exchanges during the long dwell, (enhanced CCPD) provides extra dialysis and, at the same time minimizes the disadvantages of CAPD and CCPD, namely increased glucose absorption and decreased ultrafiltration. Also, CAPD patients who require a fifth exchange can perform it during the night with a minicycler (Quantum – Baxter).

Alternate regimens are easier to perform with the dialysis modalities that use cyclers, because it is impractical to perform more than 5 manual daily exchanges when one needs a higher dose or longer treatment time. On the contrary, patients seem to accept more readily an increase of nocturnal treatment time to 10 – 12 hours/day if it is carried out mainly during the hours of sleep.

Tidal Peritoneal Dialysis (NTPD)

In this method the cycler infuses a fixed volume (1.2 – 1.5 L) with rapid exchanges (4 – 6 min dwell time, 20 min total exchange time) during a dialysis session that lasts 8 – 10 hours. The infusion volume is added to a constant "tidal" volume of 1.2 – 1.5 L of solution that is maintained in the peritoneal cavity throughout the session. This tidal volume is achieved after an initial filling with a large (3 L) volume of solution; during the drain phase, only one-half of this volume escapes from the abdomen. The next fill and drain volumes are equal to the tidal volume and only at the end of the session is the peritoneal cavity drained completely; it remains empty until the next treatment. The usual dose is 26 – 30 L/session. This form of NIPD avoids waste dwell time during the initial fill and the end of drain when the peritoneal cavity is empty and no dialysis takes place.

Adequacy of PD

The primary goal of PD as renal replacement therapy is to maintain the uremic patient in the best physical and clinical condition and prevent the complications of ESRD. Assessing PD adequacy not only helps to establish the minimum dose compatible with short-term well-being and absence of uremic symptoms, but also helps define the optimum dialysis dose, i.e. the dose that provides favorable long-term outcomes to survival, rehabilitation and quality of life.

Although some uremic symptoms such as pericarditis, nausea, vomiting, and a rising BUN and serum creatinine concentration are the result of insufficient clearance of uremic toxins, there are no symptoms or biochemical findings that clearly defines PD adequacy. It is considered that such clinical criteria as a feeling of well-being in the absence of uremic symptoms, such as anorexia, nausea, and insomnia are associated with good fluid balance, normal blood pressure and biochemical status of decreased BUN < 100 mg/dL and of serum creatinine concentration < 18 mg/dL, are indices of adequate PD. Stable lean body mass, stable nerve conduction velocities, and a hematocrit (HCT) > 25% without recombinant human erythropoietin (rHu-EPO) or anabolic steroids also have been proposed as indices of adequacy.

Recently more specific methods using urea and creatinine kinetics have been described to assess the adequacy of PD, in which the dose of dialysis is determined by weekly measurements of creatinine and urea clearances.

Normalized Weekly Clearances

Weekly clearances are normalized to reflect the patient's size so as to individualize the dose of dialysis. Creatinine clearance (C_{Cr}) is normalized to body surface area (BSA) standardized for a BSA of 1.73 m^2, while the volume of body water (*V*) in which urea is distributed has been used to normalize the weekly urea clearance. The latter approach produces the parameter *Kt/V* that governs urea kinetics during hemodialysis; this symbol represents the volume of plasma cleared of urea (*K*) over a certain time (*t*) divided by the urea distribution volume (*V*), which is roughly equal to the total body water – 60% of lean body weight (BW) in men, 55% in women. In large patients, to assume fixed percentage of BW for the volume of distribution (*V*) may introduce errors and thus the Watson method [13] is used to provide reasonable approximation of the actual *V*.

Men *V* (L) = 2.447 + 0.3362 × BW(kg) + 0.1074 × Ht (cm) – 0.09516 × Age (yrs)

Women *V* (L) = –2.097 + 0.2466 × BW(kg) + 0.1069 × Ht (cm)

This formula was derived by comparing total body water measurements to simple anthropometric measurements (weight. height, age) in subjects without edema, volume deficit or ESRD.

According to the urea kinetic model, weekly *Kt/V* for urea (Kt/V_{urea}) provides an objective index of adequacy; originally adequate dialysis was defined as a weekly urea *Kt/V* > 1.9 – 2.0, while values between 1.7 to 1.9 were considered marginal. Patients in the latter range should be observed closely for signs and symptoms of inadequate dialysis. Inadequate dialysis may due to inadequate clearance of solutes, a hypercatabolic state

and/or failure to adhere to the dialysis prescription. For intermittent therapies such as NIPD, a weekly Kt/V_{urea} of 2.2 is recommended; this figure is based mainly upon extrapolation from hemodialysis and urea kinetics.

Also, several workers have proposed that adequate dialysis requires a total weekly creatinine clearance (C_{Cr}) of at least 60 L per 1.73 m^2 BSA [14 – 16]. Weekly creatinine clearance may be better than Kt/V_{urea} to assess dialysis adequacy, as a good correlation between urea kinetic analysis and clinical outcomes in patients on CAPD has not been shown [17], but this remains in debate. Until we have this confirmation, one should use both weekly values of 1.9 for urea (Kt/V_{urea}) and 60 L for creatinine clearance (C_{Cr}) as reasonable goals for continuous therapies such as CAPD or CCPD. In patients with residual renal function, weekly Kt/V_{urea} of 2.0 corresponds to 60.5 – 67.6 L/week/1.73m^2 of C_{Cr}; in the anuric patient, the equivalent is a creatinine clearance of 52.1 L/week/1.73m^2 [18, 19]. This means that, in absence of residual renal function (RRF), the theoretical adequate target for Kt/V_{urea} should be increased between 2.0 and 2.25.

Residual Renal Function (RRF)

Although RRF in hemodialysis, may be significant only for clearance of middle molecular weight and larger solutes, in PD residual renal solute clearances contribute significantly to total solute and water removal. Preservation of RRF may be particularly important to the effectiveness of long-term PD; therefore reports that PD provides better preservation of RRF than does hemodialysis are of great interest [20, 21].

To assess RRF, residual clearances (C_r) of creatinine (C_{rCr}) and urea (C_{rUr}) have to be measured. The use of both measurements instead of creatinine clearance alone provides a more accurate estimate of glomerular filtration rate (GFR) as the arithmetic mean of urea and creatinine clearances [$GFR = (C_{rCr} + C_{rUr}) / 2$], (Table 4). This is due to the different tubular mechanisms of secretion of creatinine and reabsorption of urea, and to the fact that as GFR declines the contribution of residual renal creatinine clearance to the total creatinine clearance rises disproportionally. Therefore measurement of sole residual renal creatinine clearance would lead to overestimation of GFR.

The corrected value of GFR is then added to peritoneal creatinine clearance (K_{pCr}) and normalized to 1.73 m^2 to calculate the total creatinine clearance (C_{Cr}). A residual GFR of 1 mL/min is equivalent to 10 L (1ml × 60 × 24 × 7); that may be a significant proportion of the total of C_{Cr}. Failures to account for the loss of RRF over time can lead to underdialysis even though dialysis efficiency has not been declined. The corresponding value of 1 mL/min of renal urea clearance to weekly Kt/V_{urea} is 0.25 L.

Middle-molecular-weight Toxins and the Peak Concentration Hypothesis

Early attempts to quantify PD noted that PD patients appeared to be in “comparable good health” relative to hemodialysis patients despite much lower small solute clearances. This difference was ascribed to more efficient peritoneal clearance of middle molecule weight toxins, a conclusion that seems to fit with recent knowledge that CAPD patients do as well clinically as those undergoing hemodialysis despite the lower weekly urea clearance (Kt/V) [17, 22]. In fact, the minimum recommended Kt/V for each hemodialysis is 1.2 – a

Table 4. Calculations of Weekly Creatinine Clearance C_{Cr}, Weekly Kt/V_{urea} and PCR

A)	Collection of 24-hour volumes of dialysate (V_d) and urine (V_u) and measurements of creatinine and urea nitrogen concentrations in dialysate (Dcr, Dur) and urine (Ucr, Uur) respectively.
B)	Measurement of the plasma creatinine (Pcr) and urea nitrogen concentrations (Pur) in a sample taken on the day of collection at any time in CAPD. In CCPD and NIPD the sample may be drawn in midpoint of the session (NIPD) and the daily long dwell exchange (CCPD).
C)	Calculate daily residual renal clearances (L/day) of creatinine (C_{rCrr}) and urea (C_{rUr}) as: C_{rCr} (L/day) = (Vu × Ucr) / Pcr and C_{rUr} (L/day) = (Vu × Uur) / Pur The average of the 2 measurements estimates GFR (GFR mL/min = [(C_{rCr} + C_{rUr}) /2] x1000/1440)
D)	Calculate peritoneal creatinine clearance (K_{pCr}) as: K_{pCr} (L/day) = (V_d) × (Dcr / Pcr) Calculate peritoneal urea clearance (K_{pUr}) as: K_{pUr} (L/day) = (V_d) × (Dur / Pur)
E)	Estimate patient's body surface area (BSA) to use normalize creatinine clearance: $(BSA)^2$ = Ht (cm) × BW (Kg) /3600 Estimate the volume of urea distribution in the body water (*V*) by Watson equation: Men *V* (L) = 2.447 + 0.3362 × BW(kg) + 0.1074 × Ht (cm) – 0.09516 × Age (yrs) Women *V* (L) = -2.097 + 0.2466 × BW(kg) + 0.1069 × Ht (cm)
F)	Calculate weekly creatinine clearance C_{Cr} = 7 × (C_{rCr} + K_{pCr}) and then normalized for BSA=1.73m^2.
G)	Calculate weekly urea clearance K_{prt} = 7 × (C_{rUr} + K_{pUr}) and then normalized for volume of urea distribution to give Kt/V_{urea}
H)	Calculate PCR (g/day) = 10.76 × (UGR + 1.46) = 6.49 UNA + 0.294 V Calculate PNA (g/day) = 10.76 × ((UNA/1.44) + 1.46) where UGR (urea generation rate, mg/min) = ((Uur (mg) + Dur (mg)) / 1440 and UNA (urea nitrogen appearance, g/day) = (Uur (g) + Dur (g) and V = the total body water (L).
I)	Calculate normalized PCR (nPCR) = PCR / (V/0.58) Where V/0.58 is equivalent to standard weight based on V

figure that represents a weekly *Kt/V* of 3.6, well above the minimum weekly Kt/V_{urea} of 1.9 – 2.0 in CAPD patients. Keshaviah has called this observation the "peak concentration hypothesis" [23]. This hypothesis postulates that uremic toxicity and the likelihood of developing early uremic symptoms is related more to the peak plasma levels of urea and other small uremic toxins rather than to the average value of these elements. According to this, clearances must be time averaged because CAPD is a continuous while hemodia-

lysis (HD) is an intermittent therapy. Therefore HD requires a higher *Kt/V* to reduce the peak interdialysis concentration of urea to the steady state level of CAPD. For similar reasons, patients undergoing intermittent PD require a Kt/V_{urea} of at least 2.2 because urea nitrogen concentrations peak between dialyses [24].

PD Adequacy and Nutritional Status

The correlation between Kt/V_{urea} and the protein equivalent of nitrogen appearance (PNA), also expressed as the protein catabolic rate (PCR) [25 – 27] provides indirect evidence of a link between PD adequacy and nutritional status. On the other hand, low Kt/V_{urea} values often are associated with hypoalbuminemia – a marker for malnutrition, and PCR levels < 0.9 g/kg/day are an index of decreased dietary protein intake (DPI) [13, 27]. These findings indicate that an increase in the dialysis dose (*Kt/V*) may increase DPI by increasing appetite, and may prolong the patients' survival on dialysis.

PCR can be measured from a 24-hour dialysate and urine collection (Table 4). Measurements of PCR from renal urea-nitrogen kinetics will provide an estimate of DPI. This calculation assumes that the patient is in a steady state; if so, PCR can be normalized to weight by dividing by the factor *V*/0.58 assuming as equivalent to standard weight (nPCR) [26]. PD patients with nPCR levels > 0.9 g/kg/day are in neutral nitrogen balance.

The serum albumin level is not a sensitive marker of nutritional status but it has been used as a predictor of outcome, because low serum albumin levels have been associated with an increased risk of morbidity and death in the PD population [28, 29].

PD Adequacy and Clinical Outcome

Recently a multicenter prospective cohort study (CANUSA) evaluated the effect of therapy dose and nutritional status on clinical outcome, using statistical techniques [15]. In this study decreased values of Kt/V_{urea} and weekly C_{cr} were associated with an increased relative risk of death. More specifically, a decrease in Kt/V_{urea} of 0.1 and in weekly C_{cr} of 5 L/1.73 m^2 BSA produced 5% and 7% increases, respectively, in the relative risk of death.

However, both a Kt/V_{urea} of 2.1 and a weekly C_{Cr} of 70 L/1.73 m^2 BSA were associated with a 78% expected 2-year survival rate. It has also been reported that underdialysis increases mortality in PD patients with ischemic cardiac disease or left ventricular dysfunction [22, 29]. Although we await clinical validation of these observations, they indicate the close relationship between PD adequacy and clinical outcome.

Acute and Chronic PD Prescription

Acute PD may be performed in patients with acute renal failure (ARF) when recovery of renal function is anticipated or in some predialysis patients with temporary exacerbation of renal failure.

Acute PD Prescription

After insertion of an acute, or more often, a chronic peritoneal catheter (Tenkchoff), the

dialysis prescription must be individualized to the patient and to his/her clinical situation. Acutely ill patients with unstable hemodynamic signs will need frequent re-evaluation and modifications in the composition of the therapeutic solutions.

The common duration of an acute PD session lasts from 24 – 72 hours with hourly exchanges of usually 2 L peritoneal solution.

Although many adult patients can tolerate 2 L of fluid, infusion volumes must be adjusted not only to the patients peritoneal cavity size but also to any respiratory disease and/or abdominal or inguinal hernias. However because larger infusion volumes increase water and solute removal rates, calculation of the most appropriate volume depends on the severity of the uremic syndrome. In some instances, one should arrange a gradual increase in volume every 10 exchanges from 0.5 – 2.5 L to avoid early fluid leakage.

Careful evaluation of the time required for first exchanges and the drainage volumes obtained enable one to avoid such common errors as abdominal distension due to incomplete drainage or slow filling because of kinking of the catheter.

Glucose (Dextrose) Concentration

Exchanges of 2 L dialysis solution hourly (inflow 10 min, dwell 30 min, outflow 20 min) with 1.5% glucose solutions usually gives an ultrafiltration rate of 50 – 150 mL/hour, which yields 1200 – 3600 mL/24 hours. Using a higher glucose concentration of 2.5 – 4.25%, one can remove larger volumes (200 – 400 mL/hour). In patients with pulmonary edema, 2 or 3 consecutive exchanges (without dwell time) of 4.25% glucose solution may remove up to 1000 mL/hour.

Dwell Time

Decreasing the standard dwell time (30 min) to 15 min and performing two 2 L exchanges/hour will increase the dialysate flow rate to about 4 L/hour (66 mL/min) and will give more efficient dialysis. These higher values are close to the maximum achievable urea clearance of approximately 35 mL/min with a dialysis flow rate of 70 – 80 mL/min. Most patients do not need high flow rates; however they may be used for short periods in hypercatabolic and hyperkalemic patients.

Complications of Acute PD

In addition to infection and acute catheter complications, acute PD may be associated with other more or less serious medical complications.

One may encounter hypervolemia, due to poor ultrafiltration rates, or hypovolemia and hypotension due to excess water removal. Often hypotension is seen with rapid hypertonic exchanges and, when it is severe, it may require temporary discontinuation of dialysis session and infusions of intravenous (IV) saline. Close evaluation of the patient's dialysis regimen, with special attention to the frequency, osmotic strength and volume per exchange can help to avoid this serious complication. Frequent (every 6 hour) blood samples may be required for early correction of electrolyte (hypokalemia) and glucose (hyperglycemia) disorders, which may accompany rapid exchanges. Potassium should be added to the dialysis solution (2 – 4 mEq/L) especially in normokalemic patients with metabolic acidosis and those who receive digitalis to prevent potentially fatal arrhythmias. IV administration of 5% dextrose in water may be required to correct hypernatremia that occurs

with hypertonic dialysis due to excess water removal because of peritoneal membrane's sieving effect.

Patients on acute PD may develop acid – base imbalance in the presence of simultaneous IV administration of bicarbonate solution because of a rapid correction of metabolic acidosis leading to paradoxical acidosis of cerebrospinal fluid (CSF), hyperventilation, and finally alkalosis. Patients with hepatic failure and slow lactate metabolism may also present with elevated plasma lactate levels.

Diabetic patients usually require additional doses of regular insulin intraperitoneally to cover the glucose absorbed during dialysis, as follows: 3 – 4 U/L for 1.5%, 5 – 6 U/L for 2.5% and 7 – 10 U/L for 4.25%. To avoid rebound hypoglycemia one should not administer insulin with the last 3 – 4 exchanges of each dialysis session. Also to compensate for dialysate protein losses (8 – 20 g/24 hours), another noticeable feature of acute PD, oral or IV protein supplementation may be required.

Chronic PD Prescription

In chronic PD, the dose of dialysis must be individualized according to the patient's BSA, RRF, peritoneal-membrane transport characteristics, nutritional status, disease-specific requirements and special clinical circumstances. Chronic dialysis prescription should specify the exchange volume, the dwell time, the number of daily or nightly exchanges, and the composition of the peritoneal fluid in order to provide the most beneficial dose. Adequate dialysis will improve the patient's outcome and the success of long-term PD therapy.

Dialysis Dose

Recent schedules recommend the targets of 1.9 – 2.0 for Kt/V_{urea}, or 60 – 70 L per 1.73 m^2 BSA weekly C_{cr} for continuous PD in patients with RRF [6]. However, with intermittent dialysis or in the absence of residual function, the adequacy indices must be increased to the range of 2.0 and 2.2 for Kt/V_{urea}, and 70 – 80 L per 1.73 m^2 C_{Cr}. It is recommended to provide the maximum dialysis that can be delivered to the individual patient, within the social and clinical circumstances, quality of life, lifestyle and cost considerations.

Initial PD Prescription

One can determine the initial PD regimen by estimating the volumes of fluid that the patient needs in order to achieve the minimal target of solute clearance. As a rule, one should use the highest tolerable volume, based on the patient's discomfort. Assuming that the patient has average peritoneal transport characteristics ($D/P_{creat} = 0.70$), the major determinants are the patient's BSA value and the RRF. Large patients often require large instillation volumes at the beginning of PD unless they have significant RRF. Accordingly, the standard prescription of four 2L exchanges may be modified (Table 5) while further clinical validation is often required [30]. However, Nolph and coworkers [31] have pointed out that a dose of four times 2 liters daily is inadequate for functionally anephric patients weighing > 65 kg. Actually, this weight is near the average of patients starting ESRD therapy.

One determines the total dialysis dose (by dialysis and residual urine) from the 24-hour dialysate and urine collection and the PET 3 – 4 weeks after initiation of dialysis. Then the dose is re-evaluated every 6 – 12 months

Table 5. Possible Initial Dialysis Regimens (Life-Style Choice: CAPD – CCPD)

	GFR (corrected C_{Cr}) > 2 mL/min	GFR (corrected C_{Cr}) 0 – 2 mL/min
CAPD		
BSA 1.7m^2	4 × 2 L/D	4 × 2.5 L/D
BSA 1.7 – 2.0m^2	4 × 2.5 L/D	4 × 3.0 L/D
BSA > 2.0 m^2	4 × 3.0 L/D	4 × 3.0 L/D nightly exchange device
CCPD		
BSA 1.7m^2	4 × 2.0 L/D (9 h/night) + 2.0 L/day	4 × 2.5 L/D (9 h/night) + 2.0 L/day
BSA 1.7 – 2.0m^2	4 × 2.5 L/D (9 h/night) + 2.0 L/day	4 × 3.0 L/D (9 h/night) + 2.5 L/day
BSA > 2.0 m^2	4 × 3.0 L/D (9 h/night) + 3.0 L/day	4 × 3.0 L/D (10 h/night) + 2X2.5 L/day

Assumptions: 70-kg male, anuric, BSA = 1.73 m^2, 4-hour D/P = 0.65, UF = 2 L. From [30].

to compensate for any decrease in residual urine by an increase in the dialysis dose. RRF is monitored at least every 3 months because the decline in RRF is unpredictable and may proceed at different rates in different patients. During the first 2 – 3 years of therapy the most likely change in total solute clearance is a change in the RRF.

Optimizing Instilled Volume and Dwell Time

Usually, to increase solute clearances, it is better to increase the volume per exchange, maintaining the dwell and diffusion time, rather than to increase the number of exchanges with shorter dwell time, unless the patient has high peritoneal transport characteristics. An exchange volume of 2.5 L allows almost all patients to reach C_{cr} and *Kt/V* targets even when they become anuric (Table 5) [30]. A fill volume of 2.5 L seems to give an average-sized individual maximal peritoneal transport, and a volume of 3.0 L suits patients with BSA > 2.0 m^2 [32]. However, one must balance the benefits of increasing clearance by increasing volumes with the risks associated with larger volumes such as

– an increase in hernias due to increased intra-abdominal pressure with larger volumes, and
– an increased peritoneal glucose absorption.

Drain time must also be evaluated because extended drainage may decrease dwell and diffusion times leading to a decrease in clearance. Volume adjustments can be made more easily with cycler-assisted CCPD and NIPD where one merely dials in the new value on the cyclers. Often the patient tolerates larger exchange volumes better on these modalities than on CAPD because most of the exchanges take place with the patient in supine position. However, most of these patients will need "wet" days, i.e. dialysate in the abdomen during the day, especially when they become anuric. Also, increased fill volumes of 2.5 L should be used to improve C_{Cr} in patients on automated PD (APD) (Table 6) [30].

Table 6. Impact of Larger CAPD and APD Fill Volumes

Method	CAPD			APD		
No of exchanges	4	5	4	6	5	4
No of exchanges (day/night)	3/1	4/1	3/1	0/6	1/5	1/4
Exchange volume (mL)	2000	2000	2500	2000	2000	2500
Volume day/night (L)	6/2	8/2	7.5/2.5	0/12	2/10	2/10
Dwell time/day (min)	270	156	270	0	720	720
Dwell time/night (min)	510	510	510	60	78	105
Total C_{Cr} (L/1.73m^2)	56.7	58.9	66.1	31	38	52

Assumptions: 70-kg male, anuric, BSA = 1.73 m^2, 4-hour D/P = 0.65, UF = 2 L. From [31].

According to recent data, changes between treatment modalities with different dwell times may affect the weekly delivered dose because with long cycle therapies such as CAPD, the ratio of weekly C_{Cr} to weekly Kt/V_{urea} is higher in a given patient than with short cycle techniques, such as NIPD. Therefore, if one changes a patient from CAPD to NIPD and the C_{Cr} is kept constant, the weekly Kt/V_{urea} will increase. In contrast, if patients change from CAPD to NIPD and keep the same weekly Kt/V_{urea}, the C_{Cr} will decrease [18].

Dialysis Solution Composition

The composition of PD solution is tailored to correct the electrolyte and acid-base imbalances and restore the normal composition of the body fluids. Most CAPD, CCPD, and NIPD solutions contain similar concentration of Na (132 – 134 mEq/L), Cl (95 – 106 mEq/L), Mg (0.25 – 0.75 mEq/L) and lactate (35 – 40 mEq/L) while Ca concentrations may range from "low" (1.15 – 1.29 mEq/L) to high levels (1.25 – 1.75 mEq/L). Higher dextrose concentrations are used to increase the daily ultrafiltration rate, depending on the patient's transport rates and clinical situation. Table 7 shows typical ultrafiltrate volumes in different PD regimens.

Clinical and Laboratory Monitoring in Chronic PD Therapy

Frequent clinical and laboratory evaluations are required after dialysis is initiated to recognize early and manage effectively any water and electrolytic disorders. Careful evaluations of cardiovascular status, clinical examinations for evidence of early peritoneal complications and accurate records regarding the medical situation and the components of the PD treatment are essential.

By the end of training period (12 – 14 days), routine clinical and laboratory examinations may be instituted (Table 8).

Medications

With the initiation of dialysis, phosphate-binding agents and water-soluble vitamins may be continued at the same doses; usually diuretics and antihypertensive agents need adjustment during the early phases of training.

Table 7. Ultrafiltrate Volumes in Various PD Regimens with 2 L Exchanges

	Exchanges			mL/exchange	Total daily UF (mL)
CAPD					
8 L/D	3 daytime	×	1.5%	3 × 200 = 600	1000
	1 nightly	×	4.25%	1 × 500 = 500	
8 L/D	3 daytime	×	2.5%	3 × 300 = 900	1400
	1 nightly	×	4.25%	1 × 500 = 500	
CCPD					
10 L/D	4 nightly	×	1.5%	1000	800
	1 daytime (14-hour)	×	4.25%	– 200	
10 L/D	4 nightly	×	2.5%	2000	1800
	1 daytime (14-hour)	×	4.25%	– 200	
NIPD (8 – 10 hour)					
15 L/D	7 nightly	×	1.5%		1500
15 L/D	7 nightly	×	2.5%		2000
15 L/D	7 nightly	×	4.25%		2500

Table 8. Laboratory Monitoring of Chronic PD Patients

Every month	Every 3 – 6 months	Every 6 months	Yearly
BUN	RRF	Nerve conduction velocity	Chest X-ray
Creatinine	24-hour urine collection	Bone mineral density	
Sodium	D/P	PTH	
Potassium	PET	EKG	
CO_2	Dialysate protein		
Ca	Weekly C_{Cr}, Kt/V_{urea}		
Mg	NPCR		
Total Protein			
Albumin			
Alk. Phospatase			
Bilirubin			
SGOT			
HCT			
Hemoglobin			

Large doses of loop diuretics (120 – 500 mg of furosemide) may increase diuresis even when urine output has fallen to 100 – 200 mL/day. Commonly diabetic patients need an adjusted dose of intraperitoneal insulin to balance the increased load of glucose.

Complications Other than Peritonitis and Exit-site Care

These complications relate to the peritoneal catheter and the presence of dialysate in the peritoneal cavity, or represent uremic organ dysfunction that develops during PD. This section will discuss the former.

Catheter-related Complications

Surgical wound infection due to contamination is a rare complication. This complication may be prevented by strict adherence to sterile surgical precautions and the prophylactic use of antibiotics against the most frequent causative organisms, *Staphylococcus aureus* and *Pseudomonas species.*

Marked *pain on inflow* of dialysis solution may due to the solution's low pH, its low temperature, to the "jet flow" from the catheter tip or to distension of the tissue around the catheter. This pain my be relieved by alkalization of the dialysis solution with sodium bicarbonate (5 – 25 mEq/L), warming the solution and a choice of lower infusion rates. Usually local abdominal pain around the incision or pelvic pain (urinary bladder) are of minor importance. However, pain that is severe, diffuse or persistent may require clinical and radiographic revaluation. *Localized outflow pain* associated with drainage usually indicates that the omentum or other tissues trap the catheter. Reflex ileus may develop after catheter insertion but usually this only lasts about 24 – 36 hours.

Visceral perforations of bowel, bladder or aorta are major complications that are associated with the blind catheter insertion method.

Bloody dialysate, which is seen frequently after catheter insertion, usually, is due to the lysis of peritoneal adhesions from previous abdominal surgery, or to peritoneal irritation. The presence of bleeding disorders predisposes to this complication. Addition of heparin to the dialysis solution (500 U/L) may prevent fibrin clot formation and possible catheter obstruction.

Dialysate Leakage (Early and Late)

Early pericatheter leakage occurs in about 7 – 29% of midline catheter implantations and in 6.5% after the commonly used paramedian insertion. Predisposing factors for this complication are age > 60 years, obesity, diabetes mellitus, chronic use of steroids, multiparity and a previous abdominal operation. It appears as either a discharge of clear dialysate around the catheter at the exit-site, as localized swelling of the subcutaneous tissue of the anterior abdominal wall or as a genital swelling due to dialysis solution infiltration. Computed tomography (CT) scan after filling the peritoneal cavity with 2 L of dialysate containing 100 mL of the radiocontrast agent diatrizoate meglumine, may help determine the source of the leak. One may stop this leak by using lower fill volumes or by temporary discontinuation of PD for 10 – 14 days. However *leakage that develops late* during dialysis is difficult to correct with conservative measures and may require surgical repair.

Catheter Malfunction (Early and Late)

During the break-in period, in about 15 – 20% of the implanted catheters the peritoneal solution will not flow out – *outflow or one-way obstruction*, or will not flow in either

direction – *two-way or complete obstruction*. Common causes of two-way obstruction are blood or fibrin clots, tissue debris or kinking of the catheter's intramural segment.

Catheter malfunction late in the course of PD can be due either to clot or fibrin debris following episodes of peritonitis or more commonly to catheter dislodgment secondary to constipation, distention of the sigmoid colon, omentum wrapping, and intra-abdominal adhesions. Clinical examination, abdominal X-rays and catheterography may reveal the cause and indicate the correct management. Conservative management includes bowel stimulation by enema and the injection of heparin either to the dialysis bag applying manual pressure, or as an aseptic "flush" of the catheter's lumen with a syringe containing 500 – 1000 U heparin in 20 mL of normal saline. Also one may infuse fibrinolytic agents (streptokinase or urokinase) into the lumen. If these measures fail, the catheter has to be replaced.

Complications Related to Dialysate in the Peritoneal Cavity

The presence of dialysate in the peritoneal cavity increases the intra-abdominal pressure from 0.5 – 1.5 cm H_2O (when it is empty) to 2 – 10 cm H_2O (after filling), and predisposes to the following complications:

– *Hernias.* The constant increase in intra-abdominal pressure may overwhelm the structurally weak abdominal sites and induce several types of hernias – *inguinal, umbilical, incisional, or epigastric;* these have been observed in between 10 – 25% of CAPD population. Except for the patient's degree of physical activity, other predisposing factors are old age, obesity, female gender, multiparity and early pericatheter leak. Because of the risk of bowel incarceration and strangulation, particularly in small hernias, they should be repaired. After hernioplasty, intermittent dialysis with small volumes or hemodialysis is instituted for 2 – 4 weeks before returning to continuous therapy.

– *Abdominal wall and genital edema.* This complication, which develops in about 10% of CAPD patients has been attributed to peritoneal defects at the site of insertion. One should suspect abdominal-wall edema when there is a sudden decrease in effluent volume, and increased abdominal girth and body weight in the absence of edema elsewhere; diagnosis can be confirmed by CT scan using 2L solution with contrast medium. If the edema is refractory to conservative measures, surgical repair of the underlying defect is required.

– *Hemoperitoneum.* This usually self-limited benign complication may appear infrequently at any time during PD therapy. In women it has been related to retrograde menses, ovulation or endometriosis, but many other intra-abdominal events may be responsible for this type of bleeding.

– *Hydrothorax.* Its clinical presentation varies from asymptomatic pleural effusion discovered on routine chest X-ray to life-threatening respiratory failure. Ninety percent of these cases are on the right side, indicating the presence of a diaphragmatic defect – pleuro-peritoneal communication. The diagnosis can be made by intraperitoneal infusion of 2 L dialysate with Tc^{99m} macroaggregated albumin and subsequent detection of thoracic radioactivity. Interruption of CAPD or pleurodesis with talc, tetracycline, or autologous blood or surgical repair have been tried with varying results.

– *Back pain.* This infrequent feature is due to spinal lordosis due to the presence of PD solution, which aggravates pre-exisiting back strain. These patients do well with night dialysis technique.

Ultrafiltration Failure

The most common type of ultrafiltration failure during CAPD therapy is associated with high solute transport and early dissipation of osmotic *gradient (type I ultrafiltration failure:* D/P > 0.8, glucose dialysate levels < 500mg/dL). Frequently it is observed during episodes of peritonitis because of an increased peritoneal membrane permeability that is usually abates as the inflammation resolves. However, ultrafiltration failure may occur in association with decreased peritoneal transport rates of small solutes as a consequence of adhesions and a decrease in peritoneal surface area (*type II ultrafiltration failure:* D/P < 0.5, glucose dialysate levels > 720 mg/dL). This complication has been attributed to severe or recurrent episodes of peritonitis and extensive adhesion formation while, in a few cases, the underlying cause may be the syndrome of sclerosing peritonitis.

The patient's ultrafiltation capacity can be diminished by leakage of the dialysate through the abdominal wall, by patient overhydration and by increased lymphatic absorption of dialysate. For diagnosis, patients with apparent ultrafiltration failure requires measurements of ultrafiltration volume and a PET study.

Although type I ultrafiltration failure can be managed by temporary cessation of PD, lowers fill volumes and a reduction of long dwell, type II ultrafiltration is refractory to conservative measures.

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From Origin to Actual Trends

Claudio Ronco and Rinaldo Bellomo

The Pattern of Severe Acute Renal Failure

The incidence of acute renal failure (ARF) is approximately 50 – 100 new cases/year/million inhabitants [1]. ARF can be community acquired or hospital acquired and it may present with different clinical patterns. ARF can be isolated as a single disease or it may be part of a more complex syndrome involving other organs. Hospital-acquired ARF is an increasingly recognized condition, ranging between 2 – 5% of all patients admitted to general medical and surgical services, and increasing up to 23% in intensive care units (ICU) [2 – 4].

When ARF occurs without additional organ dysfunction, patients are treated in renal wards with standard dialysis techniques and outcome is generally favorable. When ARF occurs in "critically ill patients", severe cardiovascular, respiratory and metabolic instability, may contraindicate or preclude standard dialysis techniques. In such conditions, patients are generally followed in the ICU and continuous renal replacement therapies (RRT) are frequently employed (Table 1).

The ICU patient is critically ill and his monitoring and life support becomes extremely complex. Vasoactive drugs are utilized to counterbalance hemodynamic instability or shock conditions; mechanical ventilation or extracorporeal CO_2 removal are often required to sustain tissue oxygenation. Cardiac support is frequently achieved not only with inotropic drugs but also with mechanical devices. ARF is a common finding in this complex clinical picture. Finally, humoral and cellular mediators of inflammation are generally present in tissues and systemic circulation at very high concentrations and this may lead to the multiple organ dysfunction syndrome (MODS) due to systemic inflammatory response syndrome (SIRS) or sepsis.

Under such circumstances, an effective RRT must provide adequate blood purification from uremic toxins, correction of fluid, electrolyte and acid-base derangements, maintenance of homeostasis, protection for the kidneys from further injury and finally accelerated recovery of renal function after ARF (Table 2).

Evolution of Continuous Renal Replacement Techniques

The evolution in the field of hemodialysis has led to a parallel development of new systems for acute RRT in ICU patients. The use of new systems and techniques has permitted

Table 1. Approach to the Management of ARF

Prevention Measures	Conservative Therapy	Substitutive Therapy
– Maintain adequate volume repletion – Reconstitute circulating plasma volume – Carefully check patient's hydration when administering potentially toxic substances – Avoid potentially hazardous and risky diagnostic procedures – Consider the use of: – Mannitol – Furosemide – Dopamine – IV infusion – Other pharmacologic support – Adjust drug dosage to GFR – Undertake all specific measures in case of possible toxic exposure	– Metabolism Restrict protein intake (<0.5g/L/day) Maintain caloric intake (30-50 Cal/Kg/day) Provide adequate amount of carbohydrate to avoid ketosis and protein catabolism. Check daily nitrogen and phosphate balance – Fluid balance Make accurate intake/output balance Restrict fluid intake (if oliguria) to maintain BW Intake = Urine output + extrarenal losses Consider weight loss due to catabolism Monitor accurately fluid infusion rate – Electrolyte and Acid-base Prevent and treat hypo-hypernatremia, prevent and treat hyperkalemia Consider body pools and distribution spaces Correct metabolic acidosis (check K and Ca) Correct hyperphosphatemia and hypocalcemia – Consider initiation and choice of the RRT	– Peritoneal Therapy Consider: Peritoneal access schedule (IPD, CAPD, TPD) efficiency and prescription Respiratory problems Peritonitis risk – Hemodialysis Consider: Access to circulation schedule (HD, HF, HDF) efficiency & prescription Cardiovascular problems Poor clinical tolerance – Continuous therapies Consider: Access to circulation (A-V or (PUMP) schedule (CAVH, CAVHD, CVVH etc.) efficiency and efficacy and prescription Extrarenal effects Good clinical tolerance

to improve efficiency both in terms of blood purification and clinical tolerance. The first objective was reached by increasing the automation of the extracorporeal circuits and the operational levels of the different techniques; the second objective was reached by means of a new generation of monitoring techniques and new machines equipped with specific interfaces and alarms.

The Beginning of Continuous Arteriovenous Hemofiltration (CAVH)

In 1977 Kramer described this new treatment [5] based on a highly permeable hemofilter connected to an artery and a vein by modified hemodialysis (HD) blood lines. The arteriovenous pressure gradient was mov-

Table 2. General Criteria for the Initiation of RRT

- Oliguria (urinary output (< 500 mL/day)
- Anuria (no urinary output for 12 hours)
- BUN ≥ 70 mg/dL
- Creatinine ≥ 6 mg/dL
- Hyperkalemia (K ≥ 6 mEq/L)
- Pulmonary edema not responsive to diuretics
- Metabolic acidosis with acidemia (pH ≥ 7.2)
- Uremic encephalopathy
- Uremic pericarditis

ing the blood through the extracorporeal circuit and no pumps were utilized. Slow continuous production of ultrafiltrate was achieved and substitution fluid was administered in postdilutional mode to maintain patient's fluid balance. CAVH was a completely convective treatment, i.e. blood purification and volume control were only achieved by ultrafiltration and replacement of the fluid lost by filtration, while diffusion (the prevalent mechanism of standard HD) was totally absent (Figure 1).

The important achievement of CAVH in the early 1980s had been the ability to treat, with an extracorporeal technique for blood purification, those very ill patients in whom severe clinical conditions precluded any other form of renal replacement (Tables 3 and 4). Furthermore, CAVH enabled centers that were not equipped with HD facilities to perform acute RRT. However, while CAVH was an excellent tool for fluid control, the technique rapidly displayed its limitations in terms of solute removal and blood purification [6]. The maximal efficiency that could be achieved in CAVH was between 12 and 18 L of ultrafiltrate/day. Assuming a complete ultrafiltrate saturation and a sieving coefficient for urea close to 1, the daily urea clearance could not exceed those 18 L/day. In a patient with an

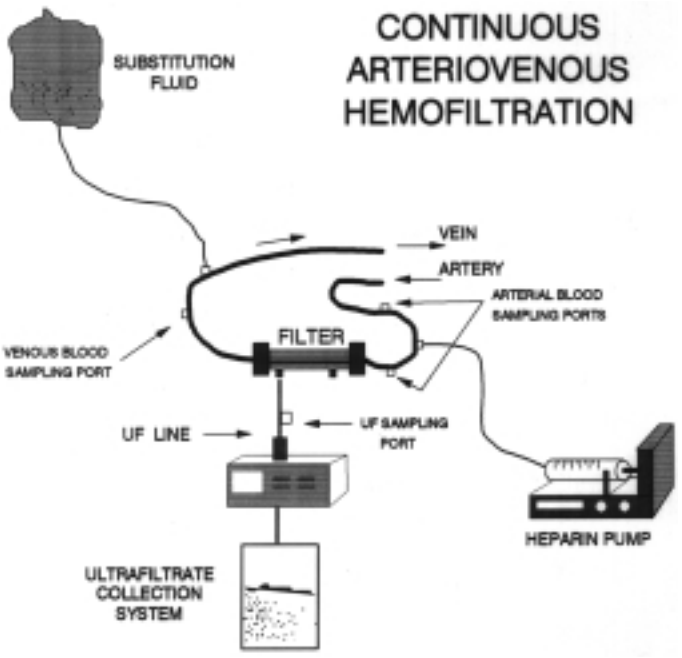

Figure 1. Schematic representation of the original CAVH Circuit.

Table 3. Intermittent Hemodialysis in Critically Ill Patients

Advantages	Disadvantages	Complications
– High efficiency – Shortness of the session – High ultrafiltration capacity – Low heparinization – Possibility to adjust therapy prescription – Clearances of drugs well known – Possibility of rapid and effective correction of hyperkalemia and other life threatening derangements	– Cardiovascular instability – High ultrafiltration /time – Need of a vascular access – Postdialytic solute rebound – Difficult solutes balance – Extracorporeal circulation – Contraindicated in hypotensive and critically ill patients – Large amounts of dialysate and replacement solutions – Body fluid and solute shifts and possible disequilibrium among body compartments – Machine required – Complex monitoring	– Infections and bacteremia – Access malfunction – Bleeding – Hypoxemia-hypoventilation – Cardiac arrhythmias – Severe hypotension – Air embolism – Disequilibrium syndrome – Worsening of brain edema – Machine dysfunction – Circuit coagulation – lines disconnection

* In chronic patients undergoing RRT, the relevant advantages and disadvantages may be significantly different

Table 4. Peritoneal Dialysis

Advantages	Disadvantages	Complications
– Cardiovascular stability – Gentleness of treatment – No need for machines – Easy monitoring – No need of heparin – Administration of nutrients – Administration of drugs – No need for vascular access – No risks of extracorporeal circulation – Steady state chemistry when CPD is performed	– Low efficiency – Low rate of ultrafiltration – Need for peritoneal access – Respiratory problems – Glucose load – Risk of infection – Contraindicated in burns and recent abdominal surgery – Large amounts of dialysate if IPD is performed – Protein losses – Increased intraabdominal pressure	– Bacterial or fungal peritonitis – Catheter malfunction – Leakage – Pulmonary atelectasis – Cardiac arrhythmias – Hypernatremia – Hyperglycemia – Intestinal perforation – Pneumoperitoneum – Hernias – Hydrothorax

average blood urea concentration of 100 mg/dL, a maximum of 18 g urea could be removed in 24 hours. Since most critically ill patients are severely catabolic, this amount of urea removal frequently resulted in an insufficient control of blood urea levels and inade-

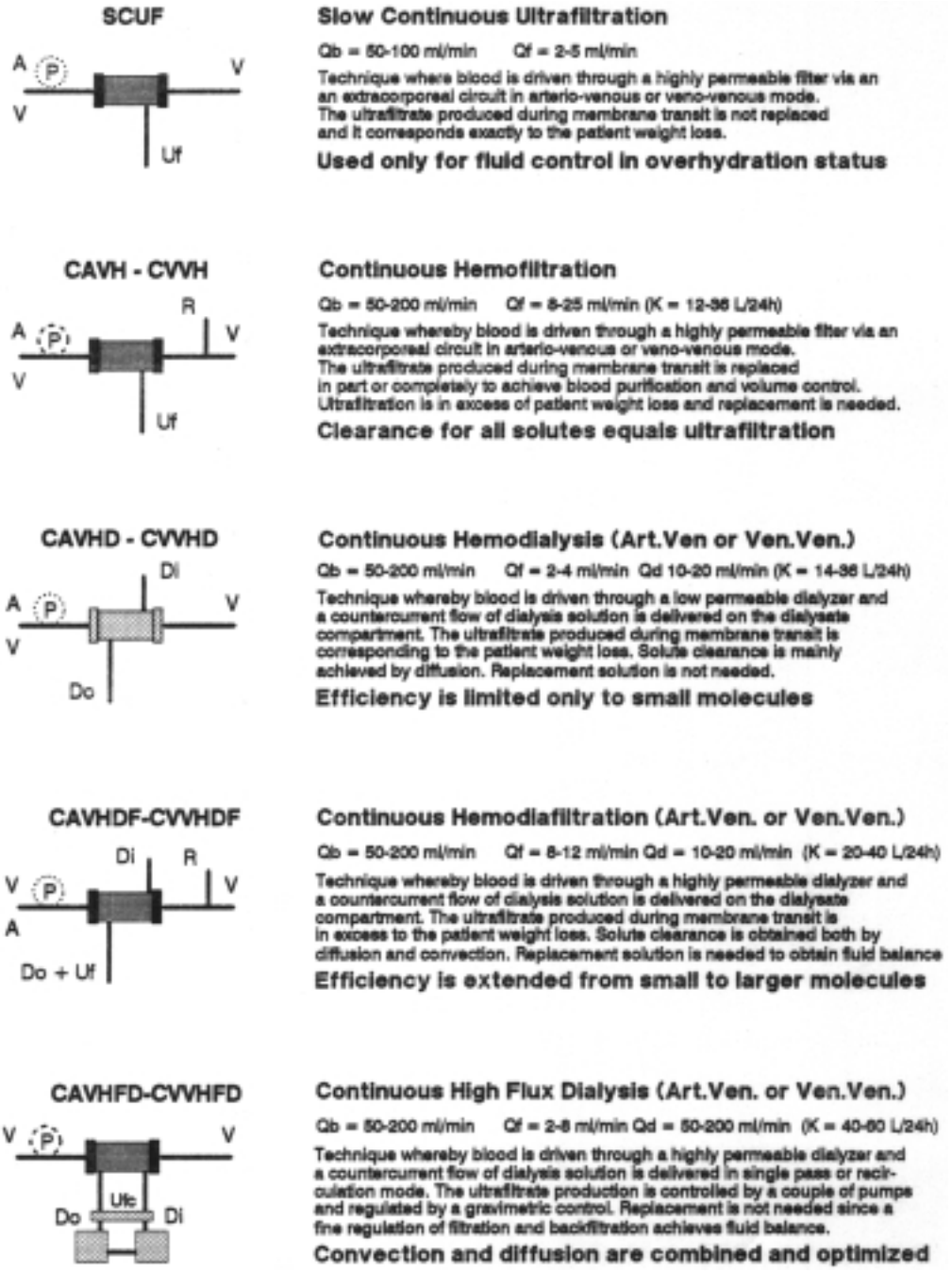

Figure 2. Schematic representation of the various techniques for continuous renal replacement therapy (CRRT). A = artery; V = vein; P = pump, R = replacement solution; Uf = ultrafiltrate; Di = dialysate inlet; Do = dialysate outlet; Ufc = ultrafiltration control system; Qb = blood flow; Qf = ultrafiltration rate; K = clearance; Qd = dialysate flow rate.

quate blood purification. For this reason, newer techniques were required and the use of continuous arteriovenous hemodialysis (CAVHD) has been introduced as a first alternative to classic CAVH (Figure 2) [7].

The treatment was similar to CAVH but a low permeability membrane could be employed and countercurrent dialysate flow was provided to increase transmembrane urea removal by the addition of diffusion. At the beginning, cuprophan (CU) hollow fiber devices were utilized, while in a second step, polyacrylonitrile (PAN) plate dialyzers were employed for CAVHD. Since a dialysate flow rate of 16 mL/min was programmed, almost complete saturation of the spent dialysate was obtained thus leading to an average urea clearance similar to dialysate flow, plus the small amount of ultrafiltration allowed from the patient. Thus a daily urea clearance in the range of 24 – 26 L could be achieved with CAVHD with an increased efficiency of treatment. In the same days, we applied the same concept to a highly permeable hollow fiber hemodiafilter, and we firstly described the treatment called continuous arteriovenous hemodiafiltration (CAVHDF) [8]. In this treatment, the higher permeability of the membrane (we were using polysulfone 0.4 – 0.7 m^2 hollow fiber hemodiafilters) allowed for a convenient combination of diffusion and convection, thus permitting not only an increased efficiency of removal of small molecules, but also an improved efficacy for the extraction of larger solutes. In our original description, a 40% increase in solute removal could be achieved in a day of treatment combining diffusion and convection. The amount of ultrafiltration exceeded the scheduled weight loss and replacement solutions had to be reinfused to maintain fluid balance.

From Arteriovenous to Pumped Circulation

One of the major limitations imposed by the arteriovenous approach was the unstable performance of the circuit due to possible reductions of extracorporeal blood flow secondary to the patient's hypotension, or circuit kinking and filter clotting. This frequently resulted in treatment interruptions, reduced daily clearance, and treatment failure. On the other hand, the perception of continuous renal replacement therapy (CRRT) had changed over time and, by the late eighties, CRRT had become more and more accepted in the ICUs as a standard form of therapy. Therefore, thanks to the recent development of double lumen venous catheters and a new generation of blood pump modules for continuous therapies, the era of CAVH started to decline and the more efficient continuous venovenous hemofiltration (CVVH) or venovenous hemodiafiltration (CVVHDF) became the golden standard (Figure 2). In CVVH, purely convective blood purification is achieved in a system where the production of ultrafiltrate is almost completely replaced by a substitution fluid. Higher amounts of fluid can be exchanged per day in CVVH, since blood flow can be maintained constant over time and the performance of the membrane is better preserved. CVVH can be performed in post-dilution mode reaching daily clearances for urea in the range of 36 L. When predilution is performed, the requirement of heparin may be remarkably reduced and ultrafiltration can be increased up to 48 – 56 L/day. It is clear, however, that since predilution decreases the effective concentration of the solute in the filtered blood, the amount of solute removal is not proportional to the volume of ultrafiltrate produced and it is reduced by a factor depending on the percentage of predilution flow vs. blood flow.

The increased amount of fluid exchanged per day in CVVH induced several units to utilize automated blood modules equipped with blood leak detectors, pressure alarms, and pressure drop measurement in the blood compartment of the dialyzer [9 – 10]. In the mean time, several machines began to use a second pump to control the rate of administration of the replacement solution and integrated systems for CVVH started to be proposed by the industry. It was clear, however, that despite the high efficiency achievable with this system, a low degree of safety and reliability was still present in these machines which were basically derived from hemodialysis blood modules but never reached the status of independent units for CRRT.

From CVVH to CVVHDF and More

More recently, a new generation of machines such as the Prisma (Hospal, Lyon, France), the Diapact CRRT (B. Braun Carex, Mirandola, Italy), EQUA-SMART (Medica, Medolla, Italy), the BM25 (Baxter Healthcare, USA) and the Multimat B-ICU (Bellco, Mirandola, Italy) have been designed as complete CRRT machines for acute renal replacement in ICU patients. These machines are all equipped with integrated safety alarms, fluid balancing controls, and connected blood modules with the possibility to perform CVVH, CVVHDF and continuous veno-venous hemodialysis (CVVHD). These machines allow smooth conduction of RRT in the ICU with increased levels of efficiency [9 – 10]. Blood flows up to 200 – 300 mL/min and dialysate/replacement fluid flow rates in the same ranges are leading to urea clearances that may reach 100 mL/min. At the same time, the highly permeable membranes utilized in these systems achieve improved clearances of the larger molecular weight solutes. Due to the higher blood and dialysate flow rates achievable in the system, higher surface areas can also be utilized and more efficient dialyzers can be applied.

The new machines are also equipped with a friendly user interface: this leads to an increased confidence of the personnel with the therapy and constant levels of efficiency can be applied without major problems or complications.

Continuous High-flux Dialysis (CHFD)

The metabolic control of ARF generally requires ≥ 20 L urea clearance/day. All attempts to add diffusion to convection have shown that, while satisfactory clearances of small molecules are generally achieved, the clearance of middle molecules might be insufficient. Since ICU patients with ARF, sepsis, multiorgan dysfunction and severe catabolism may present increased levels of substances in the middle molecular weight range (500 – 5000 Daltons), i.e. chemical mediators, vasoactive substances, cytokines such as tumor necrosis factor (TNF), Interleukin-1 (IL-1), and platelet activating factor (PAF), an adequate treatment should be oriented towards the control not only of urea nitrogen, but also of all these substances [11]. In this case the necessary amount of convection can only be obtained with high-flux synthetic membranes because of their higher sieving capacities. To come up with a compromise and to meet the requirements of adequate amounts of convection and diffusion, reduced quantities of replacement solution and easy monitoring, CHFD has recently been proposed [9 – 12].

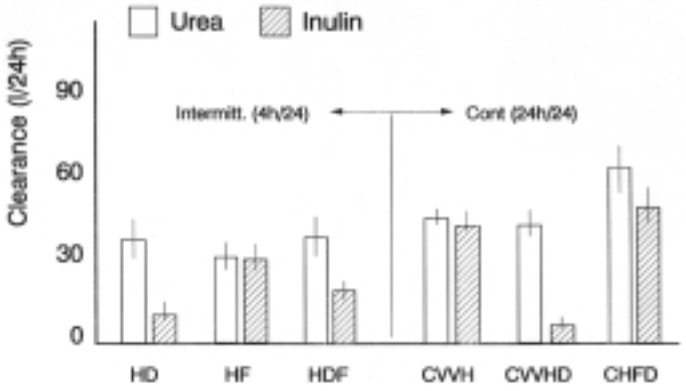

Figure 3. Efficiency of different renal replacement therapies in terms of urea and inulin clearance. (urea and inulin are taken as marker molecules for small and middle molecular weight substances respectively)

The name derives from the chronic treatment (high-flux dialysis) where a dialyzer with high permeability is utilized in conjunction with an accurate ultrafiltration (UF) control system. The UF control achieves an adequate fluid balance without need for a replacement solution. High convective transport is still maintained in the proximal part of the filter, but it is compensated by the high rate of backfiltration that takes place in the distal part of the fibers (Figure 2). This treatment has been therefore created to combine the advantages of continuous HD and continuous hemofiltration (HF).

The system consists of a circuit for continuous HD modified to achieve a continuous dialysate volume control. A hemodiafilter (or high-flux dialyzer) is utilized and 2 roller pumps are applied to the dialysate circuit. Warmed dialysate is delivered by the first pump at a programmed flow rate. The second pump regulates the dialysate outlet flow rate and therefore the net ultrafiltration, in response to a specific controller and programming module. UF control is achieved by a continuous gravimetric control. The system may operate in conditions of single pass or recirculation of dialysate. In recirculation mode, the same amount of dialysate can be better utilized with a lower cost of the treatment. In this system, once the patient's dry weight has been achieved, the circuit may operate at zero net filtration using sterile dialysate at various flows (50 – 200 mL/min). In our experiments carried out with different operational conditions and dialyzers, dialysate/plasma equilibration for urea and creatinine is reached after a variable treatment time between 120 and 210 min, when 10 L of dialysate fluid are employed in recirculation mode. Interestingly, at the same time the dialysate/plasma ratio for larger molecules such as inulin is 0.6. Assuming a continuous treatment is performed and dialysate bags are changed every 4 hours, urea clearances up to 60 L/day and inulin clearances up to 36 L/day can be expected. This represents a very efficient blood purification with a daily clearance close to or even greater than the whole urea distribution space of the patient. In this case the fractional clearance over total body water (*K/V*) approaches or exceeds the value of 1 every 24 hours (t). If CHFD is performed continuously, the weekly *Kt/V* index may be in the range of 7 – 10 thus resulting in a treatment efficiency much higher than that achieved with other intermittent dialysis therapies (Figure 3). In fact, since a steady blood urea concentration is achieved during treatment, these clearances are leading to a greater amounts of urea removal if compared to intermittent therapies where the blood con-

centrations tend to fall significantly during treatment. When less efficiency is sufficient, the bags can be changed every 6 hours and, while urea equilibration is maintained, the equilibration for larger molecules will be in this case even higher. The high clearance for inulin is mostly achieved because of the convective transport taking place in the proximal side of the filter. Zero net filtration is in fact achieved thanks to a mechanism of proximal filtration and distal backfiltration. CHFD is therefore a hemodiafiltration-like system, where the ultrafiltrate is produced in the first half length of the fibers and the reinfusion is provided in the second half by the backfiltration of sterile dialysate. Variable increases in clearances can also be achieved if the system is applied in single pass conditions with large hemodiafilters. Furthermore, some newly designed machines are able to handle 20 L of fluid and therefore bags do not need to be exchanged as frequently.

High Volume Hemofiltration (HVHF)

Recent experimental findings have demonstrated the beneficial impact of increasing the volume of UF during continuous hemofiltration therapy [13]. In particular, hemodynamic improvement has been observed in the experimental animal injected with endotoxin. Although the possibility of preventing the septic shock syndrome in humans by this technique has not been proven yet, there is enough evidence that suggest the need for a pilot controlled randomized trial to test this hypothesis. To perform HVHF, however, a clear definition of the operational ranges of the technique and a precise description of the technical requirements imposed by this form of therapy are definitely needed.

According to present clinical practice, CVVH is generally performed with an average UF rate between 1 – 2 L/hour. Above 50 liters per day, the amount of UF is considered high and the treatment can be defined as HVHF.

There are 2 ways to perform HVHF: the standard CVVH treatment schedule is maintained and the rate of UF is maintained at 3 – 4 L/hour; or the standard CVVH therapy is maintained overnight, but during a few hours of the day, a large amount of UF is produced at rates > 6 L/hour. In both cases the amount of UF exchanged per day may exceed 60 L.

Technical Notes

Continuous therapies require special care and a series of specific measures to permit smooth and safe conduction of treatment.

Access to Circulation

CAVH was performed by placing large bore catheters in an artery and a vein to guarantee a sufficient arteriovenous pressure gradient to move the blood through the circuit. Several problems including hematomas, low blood flows, and low efficiency of treatment induced most groups to move towards venovenous pumped extracorporeal circuits.

Since arteriovenous HF has been almost abandoned, the developments in the field of vascular access mostly concern venous catheters. The use of double lumen venous catheters has practically solved the problem of vascular access, permitting the use of a single head blood pump [14]. Further studies should, however, be devoted to improve the clinical

tolerance to these catheters. In particular, special care should be placed to avoid skin infections or septic problems derived from the catheter itself. Subcutaneous tunnelling and exit site care represent adequate measures to achieve such results.

Double lumen catheters however may present a series of limitations due to their design. First of all, access recirculation cannot be avoided and, in some cases, this can reach dangerous levels. When recirculation exceeds 20%, hemoconcentration takes place in the extracorporeal circuit leading to an increased viscosity of blood and easy clotting of the system. Furthermore, the efficiency of the system may be dramatically reduced leading to inadequate blood purification. Access recirculation tends to increase as the blood flow increases. For this reason, blood flows > 150 – 200 mL/min are discouraged when double lumen catheters are utilized. However, since higher blood flows may be required in some cases to achieve higher volumes of fluid exchange, 2 separate venous catheters may be the solution in such conditions. Encouraging results have been obtained with the new split-catheters.

Circuitry and Equipment

When arteriovenous HF was used, special care had to be applied to reduce any resistance in the extracorporeal circuit. For this reason, ultrashort blood lines were created and short circuits were recommended (Figure 1). The use of a blood pump in the extracorporeal circulation has essentially removed such concerns, leading, however, to an increased complexity of the circuit. A bubble trap with active alarms is necessary to avoid air embolism. Pressure measurements before and after the filter are required to avoid vessel damage or circuit explosion (Figure 4).

In modern equipment, continuous measurement of the pressure drop inside the filter, obtained from adequate pressure measurements, achieves monitoring of filter function and detection of early clotting of the fibers.

Standard blood pumps for HD have shown to be inadequate for continuous therapies and a new series of machines specifically designed for CRRT have now been created.

The ideal machine should have a small volume, an easy interface and high flexibility (i.e. the ability to perform all types of treatments). The machine must be self-standing and easily transportable to the bedside. When a new machine is designed, a certain compromise must be reached between simplicity of use and flexibility of performance. For example, the number of pumps may vary from 1 – 5 depending on the functions of the system. A single pump apparatus may be designed assuming that fluid balance is achieved by gravity or external devices, heparin administration is performed periodically, in a different intravenous (IV) line, or with an external syringe pump. Finally, the single pump may often preclude the use of a single lumen catheter in a push-pull mode. The advantage of such systems, however, is the simple layout of the circuit and the easy interface with the operator. Such systems can be operated by nursing personnel without need for long training and learning procedures. Recently, new machines for CRRT have been designed with 4 – 5 pumps. Two pumps are utilized for blood flow (single or double lumen catheters) and 2 pumps are utilized for the ultrafiltrate and replacement in CVVH mode, or for inlet and outlet dialysate in CVVHD mode. The fifth pump is utilized for heparin or drug infusion. Despite maximal simplification or self-learning display, the layout of the lines is complex and a dialysis nurse is often required. Such machines are not utilized on daily basis, and, in some cases, the training of nursing person-

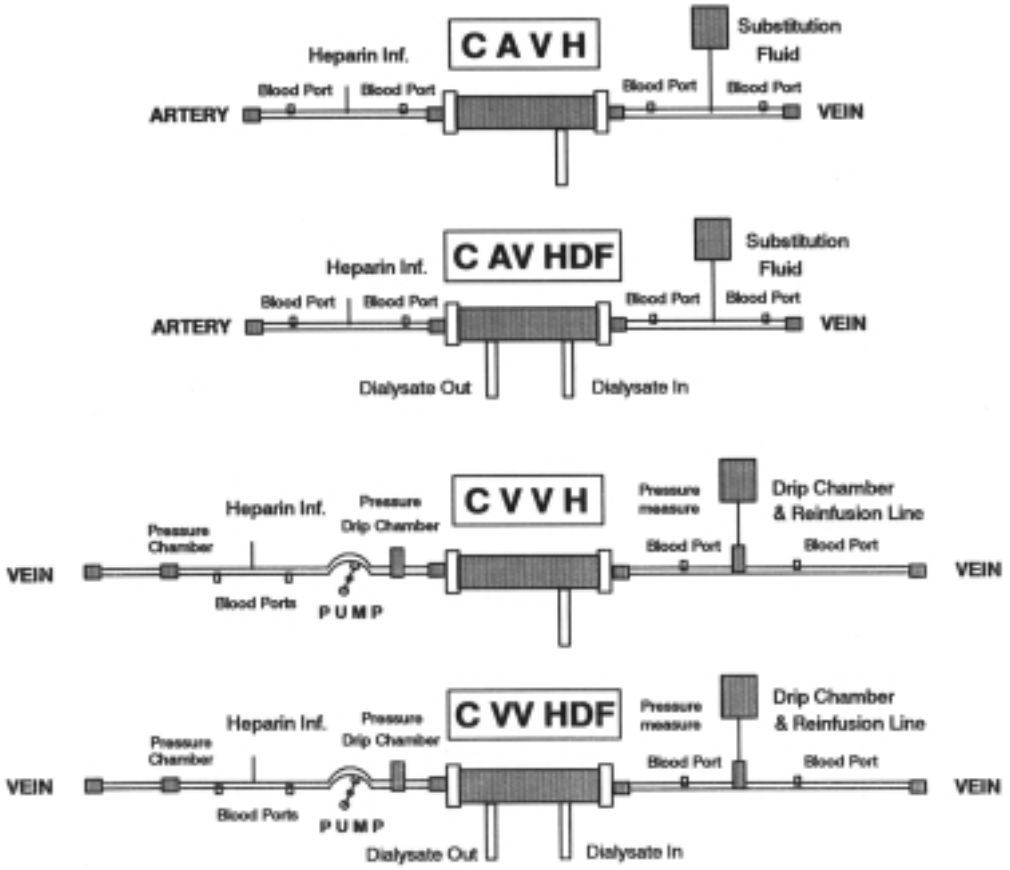

Figure 4. A series of typical CRRT circuits with blood and dialysate lines.

nel becomes difficult or prolonged. Furthermore, such machines are frequently big, difficult to move, and require costly maintenance. The cost of the lines and the entire treatment, including the machine, may significantly increase. The advantages of such systems, however, are represented by the possibility of carrying out all different treatments in the presence of any type of vascular access. Fluid balance is accurate and treatment is standardized, allowing the highest levels of efficiency and tolerance. All these machines utilize sterile dialysate. Recently, bicarbonate-based replacement fluids or dialysis solutions have been made available for this purpose. Acid and basic solutions are mixed before the treatment to avoid calcium precipitation during storage and stability of the solution is guaranteed up to 48 hours. The fluid can be warmed on line and it can be used both as a replacement solution or dialysis fluid.

Hemofilters and Dialyzers

In arterio venous HF the resistance of the hemofilter was a critical point to achieve adequate blood flows even in the presence of low arterio venous pressure gradients. For this

reason small short filters with a large cross-sectional area were identified as ideal devices for CAVHF. The search for an optimal compromise between surface and resistance has now become less important because of the extensive use of blood pumps. Blood flow is standardized and the filtration fraction (the ratio between UF and plasma flow rate) can be adjusted at the desired level in order to achieve optimal performance of the filters. High filtration fractions are leading to protein concentration polarization, and membrane clogging; therefore predilution is often used to minimize the increase in protein concentration inside the filter, and filtration rates are optimized at an average value of 20%. Anticoagulation is then achieved with lower amounts of heparin and in some cases, treatment can be carried out with no heparin at all.

All filters are now equipped with 2 ports in the ultrafiltrate compartment so that dialysate can be circulated when required. Filtration membranes have been improved beyond hydraulic permeability to achieve satisfactory diffusive properties. These membranes are in a continuous process of evolution towards reduction of thickness (i.e. reduction of diffusive resistance), optimization of pore size and distribution, hydrophilic structure, and biocompatibility properties.

Biocompatibility has been recently shown to improve patient survival and recovery of renal function [15]. Similarly, highly permeable membranes have been shown to adsorb and filter high amounts of chemical mediators of inflammation and sepsis [16 – 18]. These properties must be further explored, but they may represent a useful mechanism of renal support in critically ill patients.

Heparin-bound surfaces are still under evaluation, but this approach may further improve the biocompatibility of the membrane and reduce the risks related to heparin infusion including bleeding and heparin-induced thrombocytopenia. Substances other than heparin have been bound to artificial membranes in order to permit selective adsorption of certain molecules. This may represent an interesting therapeutic approach for the future.

Finally, when high volumes of ultrafiltrate are produced, it may be of interest to investigate the possibility of regeneration and reinfusion of the ultrafiltrate by on-line production of pyrogen-free replacement solutions from dry concentrated salts.

Clinical Aspects and Indications

Blood Purification

When continuous HF is utilized, solute clearance is equal to the amount of ultrafiltrate obtained over 24 hours. Assuming in CAVH a maximal clearance of 16 L, in a given patient with 100 mg/dL of blood urea nitrogen (BUN), 16 grams of urea nitrogen can be removed daily. When severely catabolic patients are involved, higher amounts of ultrafiltrate are needed to control azotemia and CVVH is frequently used. In such conditions clearances up to 30 – 40 L/day are required and the use of a blood pump in the circuit can achieve the desired level of efficiency. Urea is also effectively removed when a countercurrent flow of dialysate is utilized in the circuit and diffusion is added to convection, thus obtaining a treatment defined as CVVHD or CVVHDF: the first utilizes a low-flux membrane while the latter uses a synthetic high-flux membrane.

Solute concentration rebound as those seen after highly efficient intermittent treatments

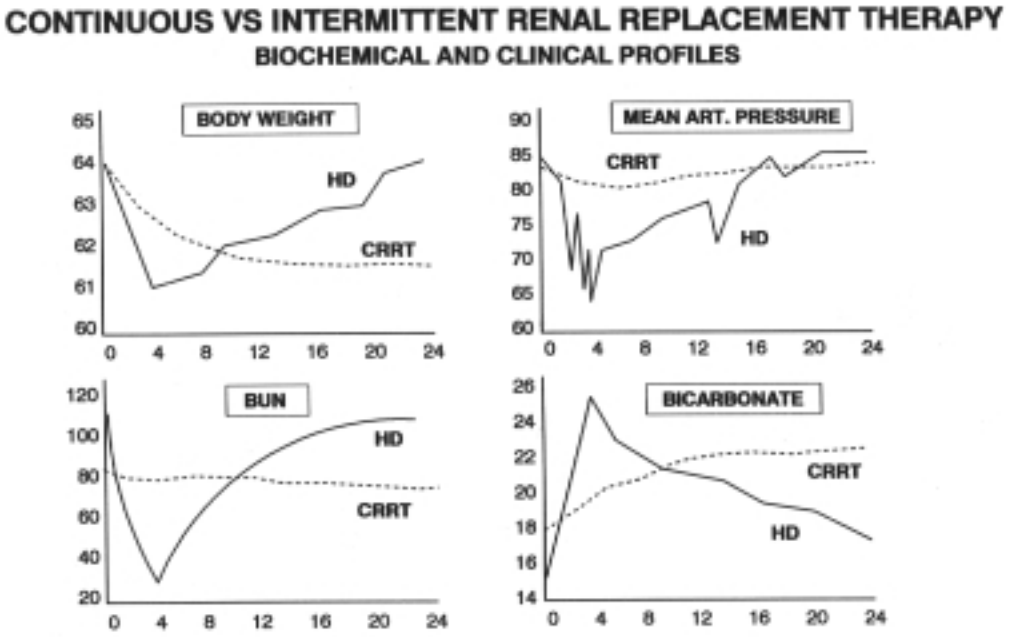

Figure 5. Continuous versus intermittent renal replacement therapy. Continuous venovenous hemofiltration is compared to intermittent hemodialysis in a critically ill patient. Continuous therapy allows for a steady control of body weight, BUN, Bicarbonate and mean arterial pressure while intermittent hemodialysis leads to remarkable fluctuations in the same parameters.

are not observed in continuous therapies; this represents a major advantage in terms of BUN time average concentration. While in intermittent hemodialysis BUN concentrations suddenly fall after one hour of treatment and solute extraction is reduced showing a remarkable postdialytic rebound, BUN concentrations are steadily controlled with continuous therapies and the average concentration over time is lower (Figure 5).

Fluid Overload, Heart Failure and Septic Shock

Clinical conditions other than ARF, such as congestive heart failure (CHF), Acute Respiratory Distress Syndrome (ARDS) and cerebral edema may benefit from continuous treatments when oliguria or early signs of renal insufficiency are present (Table 5).

The patient with severe hemodynamic instability cannot be controlled with intermittent treatments such as HD or hemodiafiltration carried out for 3 – 4 hours/day. On the other hand peritoneal dialysis (PD) cannot achieve the UF volumes and solute clearances necessary to control overhydration and severe catabolism. The slow continuous fluid removal achieved with continuous therapies such as CAVHF-CVVH or CAVHD-CVVHD is generally well tolerated and an optimal hydration status can generally be reached within a relatively short period of time with adequate constancy of measured hemodynamic parameters. Among the possible mechanisms that have been proposed to explain the steady hemodynamics in patients

Table 5.

Sequence of Events in Sepsis

Bacterial Invasion of the Host
Exo- and Endotoxin Presence in Blood
Activation of Humoral Pathways Response
Recognition of LPS via specific cell receptors
Activation of Specific Cellular Response
Production of Inflammatory Mediators

Clinical Consequences: Inflammation and Shock

Source of Endotoxins and Pyrogens	*Possible Therapeutic Approach*
Bacterial degradation and killing in the patient	Biological blockage of endotoxin (???)
Possible external contamination of the circuit	Endotoxin adsorptlon onto artificial membranes
Backdiffusion and backfiltration of LPS fragments	Endotoxin elimination by plasma filtration procedures
Signalling and cell activation without endotoxin	Intervention on endotoxin-induced biological effects
Additional transfer stimuli from membrane bioincompatibility	Modulation of humoral response
	Modulation of cellular response
	Clearance of mediators of inflammation

undergoing fluid removal by continuous HF, continuous fluid withdrawal from the interstitium with progressive vascular refilling that avoids significant relative blood volume changes has been considered a critical one (Figure 6).

This feature is particularly useful in patients with severe cardiac failure. Several mechanisms have been considered important in the amelioration of the hemodynamic conditions of patients with CHF treated with continuous HF: the improvement in ventricular filling pressures, the reduction of preload, the maintenance of the blood volume, the modulation of the renin-angiotensin axis, the reduction of afterload, and the possible clearance of myocardial depressant substances. Another factor considered important has been the possibility of a dissociation between sodium and water transport during HF. This, together with the isotonic characteristics of the ultrafiltrate, may lead to continuous vascular refilling and an improved hemodyamic conditions.

There is human and experimental evidence to indicate that continous HF beneficially affects cardiac function both in CHF and sepsis [19 – 30].

During severe CHF, fluid retention may lead to major increases in left ventricular diastolic volume. In these patients, removal of excess intravascular and extravascular fluid can be reasonably expected to optimize left ventricular filling and improve cardiac output once again. The patient's clinical status can then be expected to improve at the same time. Sufficient and safe fluid removal, however, is not always easily undertaken in these patients. There often is diuretic-resistant fluid retention and concomitant renal impairment. Furthermore, the patient's condition is such that excessive fluid removal may precipitate a severe low output state. Inadequate fluid removal, on the other hand, may result in delayed treat-

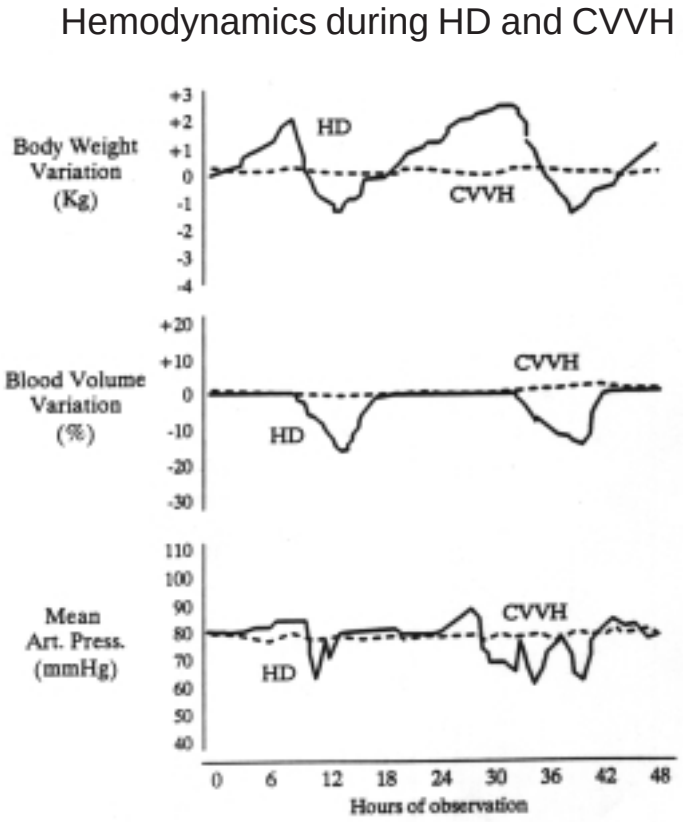

Figure 6. Continuous versus intermittent renal replacement therapy. Continuous veno-venous hemofiltration is compared to intermittent hemodialysis in a critically ill patient. Continuous therapy permits a steady control of body weight and arterial pressure. The better tolerance is explained by the absence of variation in the circulating blood volume.

ment and the development of pulmonary edema.

A possible answer to this therapeutic challenge has been provided by continous HF. The utility of such techniques in the management of episodes of refractory cardiac failure has been widely reported [19 – 30].

HF has also been shown to offer significant benefits in the setting of pediatric cardiac surgery [31], with reduced time spent on mechanical ventilation with improved hemodynamics and tissue oxygenation, accelerated recovery of renal function and significant reduction in circulating TNF, C3a – C5a and IL-6 levels.

By far the most exciting aspect of the beneficial effect of HF on hemodynamics and cardiac function pertains to the area of sepsis and septic shock. It is well known that septic shock is associated with significant myocardial dysfunction. Much evidence suggest that there may be circulating myocardial depressant substances during severe sepsis. Such depressant substances appear to have middle molecular weights and are potentially filterable. It is, therefore, possible that the use of HF in shock states would beneficially affect cardiac function. It has susequently been show that TNF is a major myocardial depressant and a likely candidate for this effect in vivo. Furthermore, it has also been recently shown that continuous HF removes TNF (and a number of other cytokines and autacoids) from the circulation of patients with sepsis [32 – 39].

Given that most removal of middle molecules during HF is convective, it is theoreti-

cally possible that increasing ultrafiltrate production and convective clearance will result in even more detectable beneficial cardiovascular effects [29 – 30]. Clearly, there is much more that we have to learn on the effect of HF in human sepsis, but its application to the management of human septic shock is already taking place particularly in the form of high-volume hemofiltration.

Recent experimental reports are promising and suggest the need for controlled studies in humans soon. Continuous HF may soon become a powerful tool in the adjunctive management of septic shock, not only to improve cardiovascular function, but also as a form of therapy directed at decreasing the effects of uncontrolled humoral inflammation on other organs.

Electrolyte and Acid-base Derangements

Continuous therapies may be used to correct water and electrolyte imbalances by changing the composition of the substitution fluids or of the dialysate. Hypo- and hypernatremia can be corrected not only by achieving a normal plasma sodium concentration, but also by restoring the normal body sodium content. Hyperkalemia can also be corrected: the efficiency in removing potassium is directly related to the amount of fluid removed during treatment and its replacement with potassium-free solutions. However, the efficiency of CAVH-CVVH in removing potassium is rather low, and continuous HD with a potassium-free dialysate may be more efficient.

Bicarbonate loss during CAVH can easily be measured directly in the ultrafiltrate or predicted using the formula:

$$[HCO_3^-]_{UF} = UF \times [HCO_3^-]_s \times 1.124$$

where $[HCO_3^-]_{UF}$ and $[HCO_3^-]_s$ are the bicarbonate concentration in the ultrafiltrate and in the serum; UF = total amount of ultrafiltrate and 1.124 = average bicarbonate sieving coefficient

When CAVH-CVVH are applied without fluid substitution to reduce fluid overload, bicarbonate losses are compensated by the reduction of the body volume distribution for the buffer and the serum concentration does not change significantly. On the contrary, when replacement solutions are infused to maintain body fluid balance, the same amount of bicarbonate lost in the ultrafiltrate must be administered to achieve stable serum levels of the buffer. Finally, to correct metabolic acidosis, the amount of HCO_3^- in the replacement solution must exceed the amount lost in the ultrafiltrate, providing a positive balance of the buffer [11]. In CHFD, bicarbonate dialysate provides an adequate buffer balance and smaller fluctuations of the acid-base status can be observed with a remarkable clinical stability.

Special Indications

In patients with cerebral edema, intermittent treatments may worsen the clinical condition because of a post-dialytic influx of fluid both in the grey and white matter. These alterations induced by intermittent treatments are not observed with continuous therapies that can therefore be utilized with maximal advantage in these patients.

Infants and neonates have been successfully treated with continuous therapies. The slow progressive action of the treatment may help achieve adequate RRT and the correction and maintenance of a homeostasis. For these treatments, special minifilters with reduced priming volumes have been utilized.

Several mechanisms have been proposed to explain the improvement of ARDS patients treated with continuous HF. Continuous fluid withdrawal from the interstitium due to isoosmotic ultrafiltration and progressive vascular refilling represents a major advantage. However, the modulation of vascular inflammation thanks to the clearance or adsorption of specific pro-inflammatory substances onto the membrane has been recently hypothesized. This mechanism has also be invoked as an interesting therapeutic possibility for patients with SIRS (systemic inflammatory response syndrome) or septic shock (Table 5).

Beyond RRT and Towards Renal Protection

Recently, several studies have provided evidence for inflammatory mediators to be of relevance in determining structural and functional changes capable of establishing ARF. Eicosanoids, cytokines (TNF, IL-1, IL-6, IL-8), endothelin (ET), and PAF may all contribute to the fall in renal blood flow (RBF) and GFR during sepsis.The biologic properties of these mediators alone or in combination may account for the metabolic and hemodynamic changes of sepsis.

Evidence that excess of TNF-α and/or IL-1β may be causally involved in the development or sepsis-induced MODS raises the possibility that removal of these cytokines from the circulation of clinically ill patients may be of benefit. CVVH provides extraction of significant quantities of circulating macromolecules (molecular weight 30 kilodaltons) with high permeability membranes currently in use. We have shown clearances of 30.7 and 36.1 L/day for TNF-α and IL-1β with a total excretion rate (ng/day) of 14.1 and 10.6. Excretion was mainly by ultrafiltration, although other authors have envisaged significant absorption by hydrophobic membranes. The relevance of convection in maximizing the performances of filter systems cannot be overemphasized and may cast doubts on studies where it might have been overlooked. However, several aspects have to be clarified before the extracorporeal removal of cytokines can be unanimously accepted as clinically relevant. First, TNF-α and IL-1β are not the sole cytokines to play a role in septic shock. Second, the incidence of detection of TNF-α in septic patients is variable and the concentration of IL-1β is usually not increased. Furthermore, IL-8, another important pro-inflammatory cytochine, is not ultrafiltered by all high-permeability membranes. The second aspect is the high "volume of distribution" and high endogenous clearance of cytokines. Much interest has recently emerged over membrane handling of different mediators. Deeper insights into the mechanisms at work may provide new ideas for more appropriate surfaces and dialytic strategies. We have already hinted at the relevance of convection in the removal of mediators of sepsis.

In a recent study, we evaluated the removal of PAF by experimental CAVH with respect to kinetics, absorption and ultrafiltration. These studies emphasized the role of plasma in enhancing removal of PAF from the distribution volume. In fact, removal of PAF by UF was significantly higher in the presence of plasma than in washed blood. Since PAF was absorbed onto the cell surface, plasma (which may bind one-third of the amount of PAF added to whole blood) may be relevant in rendering PAF available for UF. Moreover, PAF was ultrafiltered at a much lower rate when we used plasma-free washed blood cells suspended in physiologic concentrations of albumin instead of whole blood. These studies

suggest that convection in this setting increases the surface area available. Indeed CAVH membranes may function in vivo as "sponges" for mediators such as PAF and, as elsewhere demonstrated, for TNF. High amounts of PAF have been recovered from hemofilters used in patients with septic shock.

Possible advancements in the extracorporeal device dedicated to critically ill patients should take into account the need for higher convective rates , type of reinfusate, and removal of protein-bound cytokines.

Complications

Continuous therapies are generally well tolerated with a low rate of complications (Table 6) [40]. The outcome is partially related to such aspects as the severity of the illness, and the presence of concomitant factors such as mechanical ventilation or artificial cardiovascular support. The number of organs involved in the syndrome appears to be critical to the final outcome and the rate of mortality. In most series, mortality is still > 50% for critically ill patients treated with continuous therapies. As continuous HF is an invasive technique, certain typical risks have to be considered. The most severe complications were mainly associated with the arterial access in CAVH. Venovenous access reduces the complication rate considerably. Bleeding transcutaneous punctures and introduction of a large cannula by the modified Seldinger technique may lead to bleeding and even vessel perforation.With careful technique and experience, this happens only rarely.When local atherosclerosis is present, serious bleeding may occur by injuring the vessel wall and detaching plaques. Therefore, in suspected severe local atherosclerosis another access (e. g. venous) is preferred. During the course of HF, careful control of the anticoagulation (low-dose heparinization) reduces the risk of bleeding. However, at the end of the procedure, bleeding may even result from the removal of the arterial cannula. Careful and persistent compression is mandatory. If bleeding continues, the decision for surgical intervention should be made without further delay. The infection of a large persistent hematoma may cause an abscess which is difficult to treat the femoral region.

Table 6. Continuous Arteriovenous Hemofiltration vs. Intermittent Hemodialysis

- Slow continuous therapy and fluid removal
- Purely convective solute transport
- High biocompatibility of the system
- High sieving capacity of the membrane
- High adsorbtive capacity of the membrane
- Isotonic ultrafiltration
- Good clinical tolerance and hemodynamic response
- Possible manipulation of extracellular fluid composition with different substitution fluids
- No rebounds in solute concentrations -stability of the desired body hydration
- Possibility of hyperalimentation

Local thrombosis at the arterial cannula site occurs rather often (about 10%). Occasionally, this may critically restrain the perfusion of the leg; prompt surgical intervention is mandatory. Therefore, frequent and regular assessment of perfusion (e. g. by Doppler sonography) is highly advisable. Especially in severe atherosclerosis, local thrombosis becomes a considerable risk.

Local infections at the cannula site (especially infected hematomas) are serious complications because they may threaten arterial perfusion. Therefore, the extracorporeal circuit must be handled with extreme care: sterile handling with avoidance or reduction of disconnections for blood sampling.

At the high perfusion rate of the extracorporeal circuit (especially in the absence of alarms and monitoring), any accidental disconnection of blood lines acutely threatens life. Therefore all connections must be tightly locked in, and the whole circuit must be freely visible (e. g. not covered by blankets). Continuous surveillance by a competent nurse must always be ensured. It is generally accepted that the risk of technical complications clearly correlates with competence and intensity of nursing care.

Air embolism in modern pump driven systems is prevented by special monitoring and alarm systems which immediately stop perfusion when air enters the system. Except in cases of technical defects, this safety system excludes any air embolism. However, in the spontaneous CAVH technique without any alarm systems air embolism can indeed occur when a disconnection happens at the venous access and negative inspiratory pressures sucks air into the venous system.

Accidental fluid overload is a consistent danger of continuous HF techniques, especially, when a high fluid turnover is maintained. Meticulous monitoring and protocol-based assessment of fluid intake and output is mandatory. Everybody must be aware of the danger of possible fluid balance errors. Furthermore, the clinical condition of the patient must be carefully taken into account.

Hypothermia can occasionally occur when large amounts of ultrafiltrate are exchanged but simple warming of substitution fluid may correct this problem. On the other hand, continuous HF can effectively be used to reduce body temperature in cases of hyperthermia.

Hypophosphatemia has been observed and, as for other electrolytes, nutrients and drugs, solute imbalances can easily be avoided with frequent monitoring of ultrafiltrate and plasma concentrations and adjustments of the replacement fluid composition.

Treatment Outcome in Patients with ARF

Isolated ARF (e.g. caused by nephrotoxins, infections, and other renal diseases) generally has a good prognosis, with mortality reported < 10%. However, in critically ill patients treated in intensive care units, ARF is usually part of multiple organ failure arising during the hospital stay and treatment, often following complicated surgery and induced by sepsis. Here, mortality still remains extremely high, depending upon the number of other failing organs. Thus, mortality cannot directly be connected to renal failure, but is, in fact, the result of the multiple organ failure as a whole. Sepsis is the major cause of death in up to 70% of patients with ARF. Once multiple organ failure is established with respiratory and cardiovasculatory support, renal failure becomes only one problem among others. It seems therefore rather pointless to assign the mortality to ARF alone. Consequently, the positive effects of RRT cannot exclusively be compared and measured by mortality. The fact that the mortality of ARF in critically ill patients cannot significantly be improved yet, has often been used as an argument against CRRT. However, this is inappropriate. For correct comparison we need reliable methods for comparing the severity of illness of the patients involved. Scoring severity of illness, for instance by APACHE II or III, by simplified acute physiological score (SAPS), by mortality probability monitoring (MPM) or organ system failure (OSF), may help to prove the effect of renal support therapies. But, even then, all measures applied in the intensive care for the treatment of the multiple organ failure will contribute to the final outcome. In large studies from ICUs, including large numbers of patients with well-defined organ system

failure, the strong correlation between the number of failing organ systems and mortality has been clearly demonstrated: 2-organ failure for more than one day increased the death rate to 60%; 3-organ failure for > 3 days had a mortality of 92%. Furthermore, mortality tends to be higher in patients with ARF and poor previous health status, need for mechanical ventilation, and the presence of oliguria.

Certainly, scoring systems are a necessary tool for measuring severity of illness in controlled clinical trials. However, scores should not be used for decision on therapeutic interventions in individual patients. In the individual cases, prediction of outcome cannot be made from the severity of illness. Nevertheless, scores may help the intensivists have a better idea of what they were dealing with in an individual patient.

Conclusion

The above mentioned procedures represent a variety of reliable and efficient techniques for the treatment of patients with ARF. Some specific advantages such as simplicity, easy monitoring, and easy institution make CAVH a first choice treatment in several clinical conditions. For patients with severe cardiovascular instability, multiorgan failure or polytrauma, CAVH/CVVH may be the ideal treatment [41 – 45]. One of the main features of CRRT today is the flexibility of materials and techniques. Machines and devices can be utilized both for pure convective therapies and for combined diffusive-convective treatments without any complication. The circuit can be used with a blood pump or in arteriovenous driven mode. The choice of the technique and materials will therefore depend on the patient's clinical requirements, the hospital facilities, and the knowledge and training of the nursing staff. The institution of the above described procedures and the use of new devices and materials can now overcome the classic limits of low depurative efficiency or frequent clotting of filters and will make the use of CVVH and related techniques more and more common in the treatment of critically ill patients. The new possibilities offered by different membranes in terms of removal of special pro-inflammatory substances open the horizon to newer indications for extracorporeal blood treatment, such as the treatment of sepsis, multiple organ failure, and other pathologic conditions. Finally, the possible use of extracorporeal blood treatment to protect kidney function or to shorten oliguria and accelerate renal recovery represent a new challange for the coming years [46].

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Plasmapheresis

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Introduction

Pheresis is derived from a Greek word that means “to remove a part from its whole”. The term “apheresis” refers to an extracorporeal procedure in which blood separator technology is used to separate and remove either the formed elements (cytopheresis) or plasma (plasmapheresis) from whole blood. In plasmapheresis or therapeutic plasma exchange (TPE), large quantities of plasma are removed from a patient and replaced with fresh frozen plasma, albumin solution and/or saline.

Originally offered as a discontinuous therapy using centrifugal techniques, over the last 2 decades TPE has been increasingly performed using highly permeable plasma filters and standard dialysis machines. Recently, new techniques such as cascade filtration, cryofiltration, thermofiltration, and specific immunoglobulin adsorption have been developed to improve removal of specific substances. This chapter describes the therapeutic rationale, technology and application of TPE, as well as advances in this field.

Rationale

There are several mechanisms by which plasmapheresis exerts its beneficial effects (Table 1). Its major mode of action is rapid

Table 1. Possible Mechanisms of Action of Therapeutic Plasma Exchange

Removal of abnormal circulating factor
– Antibody (anti-GBM disease, Myasthenia gravis, Guillain-Barré syndrome)
– Monoclonal protein (Waldenstrom’s macroglobulinemia, myeloma protein)
– Circulating immune complexes (cryoglobulinemia, SLE)
– Alloantibody (Rh alloimmunization in pregnancy)
– Toxic factor (TTP/HUS, FSGS)
Replenishment of specific plasma factor
– thrombotic thrombocytopenic purpura
Other effects on immune system
– Improvement in function of reticuloendothelial system
– Removal of inflammatory mediators (cytokines, complement)
– Shift in antibody-to-antigen to more soluble forms of immune complexes
– Stimulation of lymphocyte clones to enhance cytotoxic therapy

depletion of specific disease-associated factors. Examples of these factors include pathogenic autoantibodies, (e.g. anti-glomerular basement membrane (anti-GBM) antibody, antibody to myelin sheath), immune-complexes, cryoglobulins, myeloma light chains, thrombotic factors, cholesterol-containing lipoproteins, and other putative toxic mediators (e.g. focal segmental glomerulosclerosis (FSGS)). The basic premise of the treatment is that removal of these substances will allow for reversal of the pathologic process related to their presence. There is also evidence that plasmapheresis contributes to immune modulation by processes other than mechanical removal of antibodies or other intravascular compounds. For example, Lockwood and colleagues [1] have shown that the splenic clearance of autologous heat-inactivated red blood cells improves after plasmapheresis, an indication that this procedure may deblock the reticuloendothelial system and improve the endogenous clearance of antibodies or immune complexes. Another specific effect of plasmapheresis is its ability to remove other high-molecular weight proteins that may participate in the inflammatory process (intact complement C3, C4, activated complement products, fibrinogen and possibly cytokines). Many other theoretical effects of TPE on immune function have been proposed including immunomodulatory actions such as alterations in idiotypic/antiidiotypic antibody balance and shift in the antibody-to-antigen to more soluble forms of immune complexes, facilitating their clearance, and stimulation of lymphocyte clones to enhance cytotoxic therapy.

TPE also allows the infusion of normal plasma which may replace a deficient plasma component, and may be the principal mechanism of action of TPE in thrombotic thrombocytopenic purpura (TTP) [2].

Indications for Plasmapheresis

A decade ago, a writing committee appointed by the American Society of Apheresis (ASFA) developed a group of position papers to offer guidelines for clinical practice [3]. A similar report was published by the American Medical Association (AMA) Panel on therapeutic Apheresis [4]. Soon after, a National Institute of Health (NIH) Consensus Conference was convened to evaluate plasma exchange in neurologic diseases [5]. However, the recommendations offered by these panels were in part still controversial. In 1993, a writing committee from ASFA offered revised recommendations of therapeutic hemapheresis [6]. While these recommendations are a consensus of opinion of the writing committee, they are not to be construed as official ASFA policy or standards of practice. It is also extremely important to bear in mind that while the writing committee placed disorders in which therapeutic hemapheresis is at least one management option, it must be stressed that patients with the same disease present with a quite heterogenous clinical picture which leaves place for an individual treatment decision especially when conventional treatment has failed. Accordingly, the ASFA defined the following 4 categories:

– *Category I*: Therapeutic hemapheresis is standard and acceptable but this does not imply that it is mandatory in all situations. Evidence is usually derived from controlled and well-designed clinical trials.
– *Category II*: Therapeutic hemapheresis is generally accepted, however, it is considered to be supportive to other more definitive treatments rather than serving as primary therapy.

– *Category III*: Reported evidence is insufficient to establish efficacy of therapeutic hemapheresis. Only anecdotal reports are available. Hemapheresis might be used in these conditions as part of an exceptional effort for an individual patient for whom other conventional therapies have failed, or as a form of therapy being evaluated under a research protocol with IRB approval.
– *Category IV*: Available controlled trials have shown lack of therapeutic efficacy of hemapheresis and should be done only with an approved research protocol.

In this chapter, emphasis will be placed on a few diseases in which plasmapheresis has been shown to have a clear benefit (Table 2), either as primary or adjunctive therapy (Categories I and II).

When one examines the published studies on the efficacy of plasma exchange in renal diseases, several general considerations that may complicate data interpretation must be kept in mind:

– The number of diseases for which plasmapheresis has been shown to be effective in well-designed, prospective, randomized studies is small. This drawback reflects, in part, the relative rarity of most of the disorders under investigation. To compensate, many investigators have understandably grouped heterogeneous diseases, often retrospectively, and utilized historical controls. The latter design is potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improved general care over time may be misconstrued as a benefit of plasma exchange.
– The natural history of many diseases commonly treated by plasma exchange is characterized by episodes of exacerbation and remission, further underscoring the importance of adequate concurrent controls.
– The threshold for intervention and the details of treatment protocols may vary widely between centers, rendering it difficult to interpret results.
– Plasma exchange is primarily utilized in the treatment of inflammatory renal disease as an adjunct to conventional immunosuppressive therapy and might therefore be expected to confer only a small

Table 2. Indications for Plasmapheresis*

– Goodpasture's syndrome (anti-GBM disease)
– Thrombotic thrombocytopenic purpura/Hemolytic uremic syndrome
– Cryoglobulinemia
– Hyperviscosity syndrome
– Myeloma cast nephropathy
– Acute demyelinating polyneuropathy (Guillain-Barré)
– Homozygous familial hypercholesterolemia (selective adsorption)
– Myasthenia gravis crisis
– Chronic inflammatory demyelinating polyneuropathy
– Eaton-Lambert myasthenic syndrome
– Post-transfusion purpura
– Refsum's disease
– Cutaneous lymphoma (photopheresis)
– HIV-related syndromes (polyneuropathy, hyperviscosity, TTP)
– Coagulation factor inhibitors
– Rapidly progressive glomerulonephritis (without anti-GBM)
– Paraproteinemic peripheral neuropathy
– Systemic vasculitis associated with ANCA
– ABO-incompatible marrow transplant
– SLE (in particular SLE cerebritis)
– Bullous pemphigoid
– Pemphigus vulgaris
– Immune thrombocytopenia (Staph protein A adsorption)
– Hemolytic disease of the newborn

*These conditions are considered category (I) or (II) according to ASFA Writing Committee and Extracorporeal Committee of the American Association of Blood Banks, 1992. See text for details.

additional benefit that would require large sample size for its detection (i.e. multicenter trials required to establish efficacy). Finally, it is particularly important that attention be paid to timing, frequency, and rate of plasmapheresis as well as associated immunosuppressive treatment used in the studies. Often diseases that may respond to plasmapheresis have been treated with a regimen of plasmapheresis, such as once a week, that could not have shown any beneficial effects, or plasmapheresis was used without concomitant immunosuppression inducing clinical worsening, or was started too late to be effective.

Indications for Emergency Plasmapheresis

Life-threatening or organ-threatening situations that may require emergency plasmapheresis include:

- Anti-GBM disease and/or pulmonary hemorrhage in Goodpasture's syndrome. In anti-GBM disease, if plasmapheresis is initiated late in the disease (serum creatininee > 7 mg/dL or after oliguria develops), it is rare that plasmapheresis is effective;
- Hyperviscosity syndrome with signs and symptoms suggesting impending stroke or loss of vision and
- Microangiopathic thrombocytopenia [TTP/hemolytic uremic syndrome (HUS)]. TTP with central nervous system (CNS) and renal complications can be a fulminant and rapidly fatal disorder and requires the institution of plasmapheresis as soon as possible.
- Patients with very high factor VIII inhibitor levels requiring urgent surgery, to prevent post-surgical bleeding complications.
- Pulmonary embarrassment in Guillain-Barré Syndrome,
- Patients with myasthenia gravis and respiratory distress not responding to medication, and
- Acute poisoning with certain mushrooms or with other strongly protein-bound poisons such as parathion or paraquat may require emergency plasmapheresis, depending on the severity of the intoxication.

Principles of Treatment

- Because of the immunologic nature of most diseases treated by plasmapheresis, therapy should almost always include concomitant immunosuppression, i.e. in most diseases TPE should not be the sole modality of treatment. Adjunct drug protocols usually include high doses of corticosteroids and cytotoxic agents such as cyclophosphamide. These agents would be expected to reduce the rate of resynthesis of pathologic antibodies (e.g. IgG) and to further modulate cell-mediated immunity, which may contribute to many of these disorders.
- Diseases that respond to plasmapheresis are best treated early to halt the inflammatory response that often contributes to disease progression. For example, plasmapheresis of anti-glomerular basement membrane disease is most effective if therapy is initiated when serum creatinine is < 5 mg/dL.

Table 3. Distribution Volumes of Immunoglobulins

Substance	Molecular weight	% Intra-vascular	Half-life (days)	Normal serum concentration (mg/dL)
Albumin	69,000	40	29	3500 – 4500
IgG	180,000	50	21	640 – 1430
IgA	150,000	50	6	30 – 300
IgM	900,000	80	5	60 – 350
LDL-cholesterol (β-lipoprotein)	1,300,000	100	3 – 5	140 – 200

Pharmacokinetics of Immunoglobulin Removal

Since the most important rationale for TPE is removal of pathogenic autoantibodies, knowledge of the kinetics of immunoglobulin removal as it relates to TPE is fundamental. Results of experiments [7, 8] in which isotopically-labeled immunoglobulins have been infused into humans have demonstrated 3 fundamental concepts:

– (1) immunoglobulins have relatively long half-lives (t ½) approaching 17 days for IgG and 5 days for IgM. The plasma t ½ will determine how quickly the plasma level of the pathogen will rebound and *how often* subsequent plasmapheresis sessions will need to be performed.
– (2) Immunoglobulins have a substantial extravascular distribution. The distribution volumes of various immunoglobulins and their half-lives are shown in Table 3. The extent of intravascular vs. extravascular distribution will determine *how effectively* they can be removed in the course of a single plasmapheresis session. For example, the extravascular distribution of IgG is approximately 60% while that of IgM is 20%, therefore depletion of IgM occurs more quickly than IgG (Figure 1). This distinction is also probably accounted for by the substantial differences in the molecular weights (160,000 daltons for IgG and 900,000 daltons for IgM) of these immunoglobulins.
– (3) Immunoglobulins exhibit an intravascular to extravascular equilibration that is approximately 1-2%/hour while extravascular to intravascular equilibration may be somewhat faster, governed by the rate of lymphatic flow [9, 10].

The importance of these 3 concepts to clinical application of TPE is dual. First, considering the relatively long t ½ of immunoglobulins, the use of immunosuppressive agents that decrease antibody production cannot be expected to lower the levels of a pathogenic autoantibody for at least several weeks, even if production is completely blocked. This is the basic rationale for their removal by extracorporeal means. Second, since the extra- to intravascular equilibration is relatively slow, the kinetics of immunoglobulin removal by plasma exchange can be calculated by using first-order kinetics governing removal rates from a single compartment (the intravascular space).

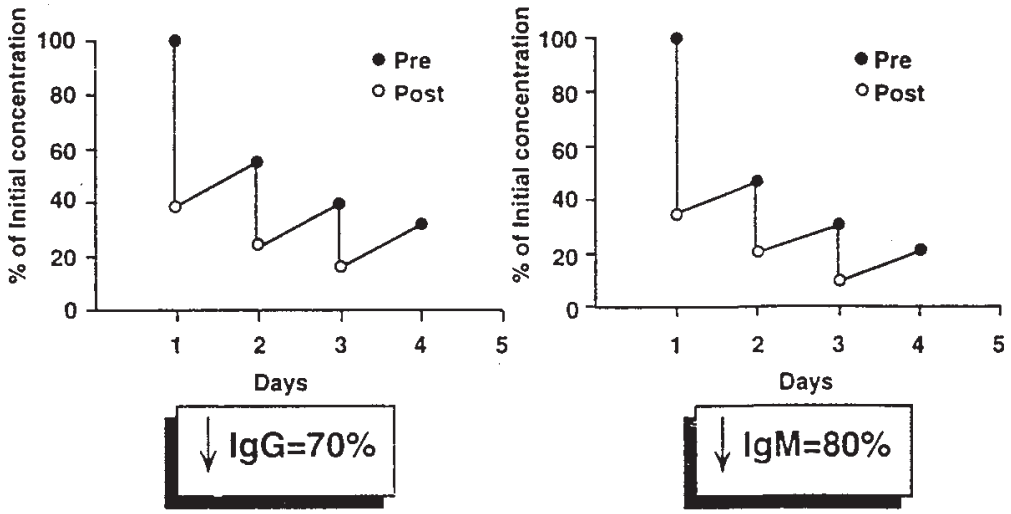

Figure 1. Percentage decline in pretreatment serum concentrations for IgG and IgM after 3 day exchanges (one plasma volume per day).

The kinetics of immunoglobulin removal by TPE follows an exponential relationship:

$$C_t = C_o e^{-x}$$

where C_o is the initial concentration of the substance, C_t is its concentration at time t, and x depends on the volume of distribution of the substance in question. This relationship implies that the largest decrease occurs with the removal of the first plasma volume and removal of subsequent plasma volumes becomes less effective in decreasing the concentration of the substance. This is shown in Table 4, if one assumes no new synthesis or redistribution during the time of plasmapheresis. As can be seen, although the removal of the first plasma volume leads to an initial 63% reduction of the intravascular concentration of the substance, the exchange of the second plasma volume leads only to an additional 25% reduction, whereas the third plasma volume exchange leads only to a further 9% reduction. *For this reason, usually one, and at most two, plasma volume equivalents are exchanged during a plasmapheresis session.*

Table 4. Relationship Between Plasma Volume Removed and Concentration of Substance

Plasma volume exchanged	Volume exchanged (mL)*	Percentage removed (%)
0.5	1400	39
1.0	2800	63
1.5	4200	78
2.0	5600	86
2.5	7000	92
3.0	8400	95

*Plasma volume = 2800 mL in a 70 kg patient, assuming HCT = 45%.

Predicting the decline in immunoglobulin levels resulting from plasma exchange is completely analogous to the *KT/V* formula used

for prescribing hemodialysis. Using this analogy, one can consider that *KT* equals the volume exchanged (*Ve*), which is the net clearance given during the treatment. *V* can be considered to be the estimated plasma volume (EPV), which is the only compartment from which immunoglobulins can be removed during a given treatment. Kaplan and Halley [9] have demonstrated a correlation between the volume of exchanged plasma and the percentage decrease in serum immunoglobulin levels, which also holds true for other large-molecular weight substances, such as cholesterol-containing lipoproteins and complement [11]. For example, if the fraction *Ve/EPV* equals 0.7, the expected decrease will be 50%. When the volume exchanged equals *EPV*, the decrease was 63% and when the *Ve/EPV* equals 1.4, the decrease would be 75%.

Subsequent to the removal of the macromolecule in question, there is a reaccumulation of its concentration in the vascular space from 2 sources:

– (1) lymphatic drainage into the vascular space, with a concentration of macromolecules that reflects its presence in the extravascular (primarily interstitial) space as well as from diffusion of the macromolecule across capillaries from interstitial to intravascular space, and
– (2) endogenous synthesis. This phenomenon has been documented in Goodpasture's Syndrome, in which the anti-GBM antibodies will be predictably lowered by a given plasma exchange treatment, but intertreatment increases in serum levels are too rapid to be compatible with simple reequilibration of extravascular stores.

Thus over the course of the next 24 – 36 hours, the vascular concentration of the macromolecule would rise from approximately 35% of basal levels immediately after one plasma volume exchange to approximately 60 – 65% of its basal concentration. A second plasma exchange of one plasma volume would then reduce it to 20 – 25% of the original concentration only to be followed by a gradual reaccumulation over the subsequent 24 hours to 58% of original concentration as shown in Figure 2. At the time of the fourth or fifth TPE, the concentration of the macromolecule would be oscillating between 10% at the end of the procedure to 20 – 25% before the next procedure [10, 12]. At this range of concentration, the efficiency of plasmapheresis is greatly reduced, and further plasma exchange is generally unwarranted.

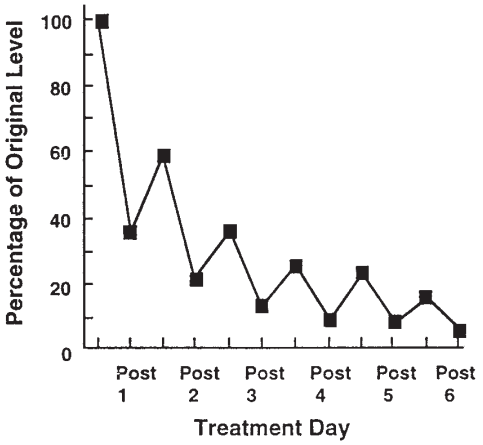

Figure 2. Plasma levels of IgG before and after plasmapheresis.

Based on these concepts, a rationale approach for prescribing TPE is generally to recommend one plasma volume exchange daily for 5 consecutive days with intervals of 24 hours, to allow for adequate lymphatic drainage into the vascular space. Clearly, the rate of accumulation and the frequency of TPE should also be targeted to the specific macromolecule that is pathogenic, if this is known. For example, whereas the half-life of IgG is approximately 17 days, that of IgM and

IgA is much shorter (5 – 7 days). Therefore, if the macromolecule in question is IgM, there may be a role for a more extended period of TPE, since the endogenous synthesis rate is expected to be higher for IgM than IgG. If the substance to be removed is measurable by reliable quantitative means (such as with specific autoantibody), then the treatment schedule should be designed to achieve a significant reduction of that substance, using kinetic considerations. If treatments are performed without identification of the offending agent, then the physician remains dependent on empiric treatment regimens.

Estimation of Plasma Volume

An estimate of the plasma volume is required to arrive at an appropriate plasmapheresis prescription. For this purpose there are several nomograms [13] and equations for the precise calculation of the plasma volume using height, weight, and hematocrit (HCT). These have been incorporated into newer versions of the plasmapheresis equipment. A useful rule of thumb is to consider plasma volume to be approximately 35 – 40 mL/kg of body weight, with the lower number (35 mL/kg) applicable to patients with normal hematocrits and 40 mL/kg applicable to patients with hematocrits less than normal.

– *Equations*: Predicted blood volume equations have been derived by curve-fitting techniques using subjects' height (cm) and body weight (kg) compared with actual blood volumes measured by isotope (albumin ^{131}I) dilution techniques:

$$PV = (1 - HCT)(b + cW)$$

where w = lean body weight, b = 1530 for males, 864 for females and c = 41 for males, 47.2 for females.

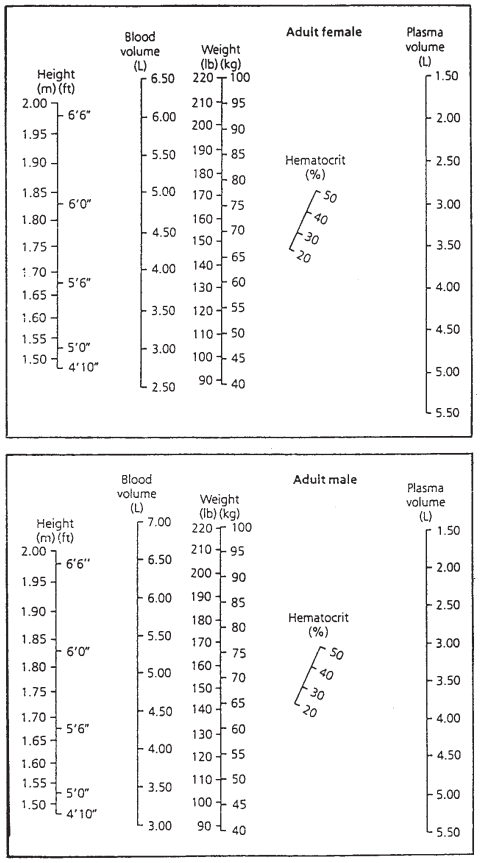

Figure 3. Plasma volume nomograms for use in therapeutic plasma exchange. Step 1: Choose the appropriate nomogram (male or female), then locate the patient's height and weight on the corresponding scales. A line connecting these points crosses the intervening scale at the patient's blood volume. Step 2: Locate the patient's centrifuge HCT level on the diagonal HCT scale. Draw a line connecting previously determined blood volume and HCT, extending it to intersect the plasma volume scale. With permission from Buffaloe and Heineken [13].

Kaplan [10] uses a simplified method for predicting the estimated plasma volume (EPV):

$$EPV = [0.065 \times \text{weight (kg)}] \times (1 - HCT)$$

– *Nomograms*: The patient's height and weight and centrifuge HCT level (mea-

Table 5. Comparison of Membrane Apheresis and Centrifugal Devices

	Advantages	*Disadvantages*
Membrane pheresis	No loss of cellular elements	Removal of substances limited by sieving coefficient of membrane
	No requirements for citrate	Requires high blood flows (> 50 mL/min)
	Can be adapted for cascade filtration	Often requires central vein catheter
		Limited to plasmapheresis
Centrifugal devices	More efficient removal of all plasma components	Loss of cellular elements of blood
	Can be adapted for cytopheresis	Uses citrate for anticoagulation: hypocalcemia, arrhythmias, hypotension
		Expensive

sured immediately before the procedure) can be entered in a nomogram for the appropriate sex to estimate the blood volume and plasma volume in 2 steps (Figure 3). Using this nomogram, for a 6 feet (183 cm) tall, 180 pound (82 kg) man, blood volume is approximately 5.5 L. If the hematocrit is 40%, this patient's plasma volume will be approximately 3.5 L.

Technical Considerations

Traditionally, plasma exchange was performed with centrifugation devices used in blood banking procedures. These devices offer the advantage for selective cell removal (cytopheresis) but are often associated with thrombocytopenia [14]. Increasingly utilized and often more efficient, TPE can also be performed with highly permeable filters (hollow fiber devices, similar to hollow-fiber dialyzers but with large pore sizes) and standard dialysis equipment, a technique often referred to as membrane plasma separation (MPS). The advantages and disadvantages of each of the techniques is summarized in Table 5.

Centrifugal Plasma Separation

In centrifugation, blood cells are separated by gravity, based on the different densities of the various components. At present, there are two types of centrifugation: intermittent and continuous. Currently available centrifugal intermittent flow cell separators are the Haemonetics Model 30, Model V50, PEX, and Ultralite. The continuous flow devices include: Cobe 2997, Spectra, Fenwal CS3000 and Fresenius AS104. While V50, AS104, CS3000, and Spectra models require no operator monitoring or intervention except changing bags, the Haemonetics Model 30 requires continuous operator monitoring and/or intervention, while the Cobe 2997 and PEX require some operator monitoring intervention in addition to changing bags [15].

– *(A) Intermittent flow separation*: In this technique, repetitive volumes of blood (200 – 300 mL of blood each time) are withdrawn from the patient, anticoagulated, and centrifuged at high speed until the plasma fraction is layered out. The plasma layer is discarded. Packed cells including red blood cells (RBC's), white blood cells (WBC's), and platelets are then returned to the patient along with the replacement fluid.

The Haemonetics Model 30 system (Figure 4) is the most commonly used and consists of a disposable bowl assembly that is available in a variety of sizes (125 mL, 250 mL, or 375 mL). The bowl has 2 parts: a stationary inner core and a rotating outer shell. Blood (taken from an antecubital or other large vein) is anticoagulated and pumped to the bottom of the bowl, where it is distributed peripherally by centrifugal forces due to rotation of the bowl assembly. The major components of blood separate according to their density: RBC's move to the outside of the bowl; plasma, the lightest component, remains at the center, where it overflows and is collected through an appropriately placed outlet port; platelets and WBC's localize between the red cell and plasma layers. Any one of these components can be collected, discarded, or reinfused.

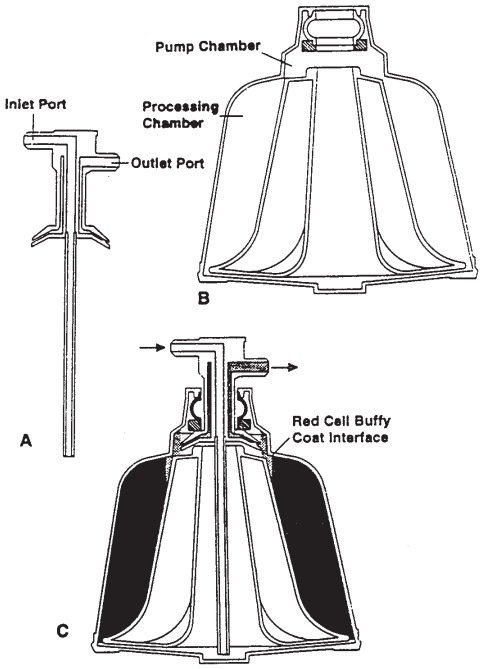

Figure 4. Haemonetics rotating bowl of plasma separation. The two subassemblies are shown. The port assembly A: remains stationary and provides the inlet and outlet ports. The bowl B: rotates at about 4800 RPM. C: the bowl after it has been filled with blood. At the point shown, the periphery of the bowl is filled with red cells, and most of the plasma, which remains in the center, has already been removed through the strategically placed outlet port (from Haemonetics Model 30 Blood Processor Operator Manual. Braintree, MA: Haemonetics Corp., 1982).

– *(B) Continuous flow separation*: In the continuous method, blood is withdrawn, centrifuged, and separated, and the packed volume is returned to the patient in a continuous mode, rather than in batches, using a hoop-shaped annulus that has sampling ports for the collection of plasma, RBCs, WBCs, and platelets.

With the intermittent systems, only a single needle vascular access is required. However, the extracorporeal blood volume is substantial (125 – 375 mL). The continuous flow system requires 2 venous accesses, but the extracorporeal circuit volume is significantly lower (80 mL), making the continuous system more suitable for treating children and patients with severe anemia. Processing time with the continuous flow system is usually faster than with the intermittent system. For example, the average time required to perform one PV exchange with the intermittent system is > 4 hours, while it takes 1.5 hours with continuous system.

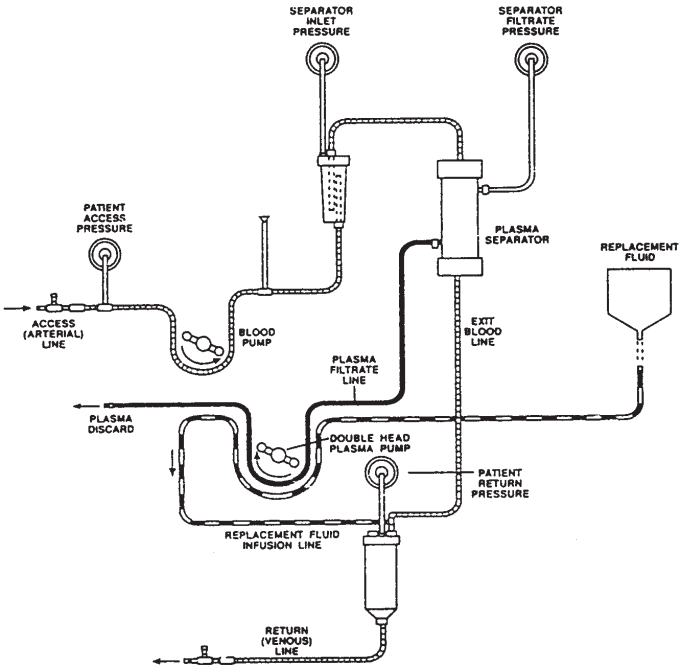

Figure 5. Circuitry for the Asahi hollow-fiber membrane plasma separator, showing the *dual-track pump* of plasma removal and replacement fluid. With permission from Apheresis Technologies [Asahi Plasma-flo Plasma Separator product literature. Apheresis Technologies, Palm Harbor, FL, 1991].

Membrane Plasma Separation (MPS)

There are 2 types of plasma membranes, hollow fiber or parallel plate. An example of hollow fiber is Plasma-flo (Asahi) of cellulose-diacetate, with an inside diameter of 340 μm, surface area 0.5 m^2, pore size 0.2 mm which allows only plasma to pass free of cells, and a sieving coefficient (ratio of concentration in filtrate to blood) between 0.8 to 0.9 for albumin, IgG, IgA, IgM, C3, C4, fibrinogen, cholesterol and triglycerides (at a blood flow rate of 100 mL/min and a transmembrane pressure [TMP] of 40 mmHg). The molecular weight cutoff of most plasmapheresis membranes is about 3 million daltons, generally sufficient to allow passage of immune complexes (MW≈1 million daltons). The Asahi plasma flow filter can be used with any dialysis machine (Figure 5) in its ultrafiltration, dialysis bypass mode (as would be used for hemoperfusion), with the possible exception of the Cobe 3 or Hospal devices which are currently incompatible with plasmapheresis tubing [10]. With the Asahi Plasma-flo separator, the manufacturer recommends treatment with a double track roller pump which allows the simultaneous removal and replacement of equivalent volumes of plasma and replacement fluid, thus eliminating the risk of hypotension or volume overload. The non-hollow fiber type of plasma membranes are the flat type sheets such as TPE Cobe Centry plasma separator (made of clear polyvinyl chloride membrane, with a 0.13 m^2 surface area, 0.6 mm pore size). The Cobe TPE system requires a dedicated plasmapheresis machine.

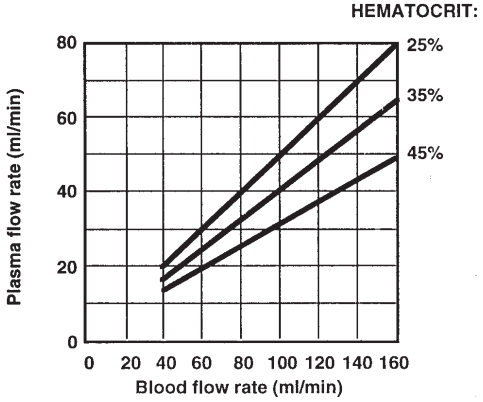

Figure 6. Relationship between blood flow rate and plasma filtration rate with the Cobe TPE flat-plate membrane plasma separator. This device automatically adjusts transmembrane pressure, which is not operator controllable (from Physician Information About the Cobe TPE System. Lakewood, CO, Cobe Laboratories, 1989).

Several excellent reviews regarding the performance of MPS have been published [16].

Contrary to hemodialysis, where ultrafiltration can be increased by greatly increasing TMP, MPS must be performed at low TMP (< 50 mmHg) to avoid hemolysis. In general, with hollow fiber devices, the blood flow rate must exceed 50 mL/min to avoid clotting. The ideal blood flow rate (Q_B) is usually 100 – 150 mL/min. When the blood flow rate is 100 mL/min, a plasma removal rate of 30 – 50 mL/min can be expected. Thus the average time required to perform a typical membrane filtration is < 2 hours. As shown in Figure 6, the plasma removal rate is linearly related to Q_B and also depends on HCT and, to a lesser extent, on TMP.

Comparison of Membrane Apheresis and Centrifugation Devices

Compared with centrifugal devices, membrane filtration has several advantages [10]. Equipment requirements are relatively minimal; only a blood pump and pressure monitors are required. MPS can thus be performed by using standard hemodialysis-delivery equipment, and patients with acute renal failure (ARF) who require hemodialysis and plasmapheresis can receive both sequentially using the same dialysis machine. MPS devices offer several other advantages over centrifugal devices (except for their inability to perform platelet or white blood cell apheresis), and are less costly. An automated continuous-flow centrifugal device costs approximately $40,000. Membrane filtration, on the other hand, requires only a blood pump with pressure monitors, which is available on every standard hemodialysis machine. Both techniques however, are roughly comparable in terms of cost per treatment (approximately $200 plus $250 – 500/treatment for blood products) [17].

Vascular Access

For the centrifuge device systems, Q_B in the range of 40 – 50 mL/min is required. This can sometimes be obtained from a large peripheral vein (antecubital vein). On the contrary, a central venous access is indicated when using MPS since a blood flow rate between 100 – 150 mL/min is required for the successful and efficient operation of the filtration system. The best approach is the use of a large bore, dual-lumen catheter similar to the ones used for dialysis especially dedicated for apheresis. The majority of intravascular devices available, such as Swan-Ganz catheters and triple lumen catheters almost never provide adequate blood flow, although they may be suitable for blood return. When using central

devices, it is very important to use blood-warming equipment if possible and monitor the cardiac rhythm due to the fact that citrate infusion (see below) causes an acute reduction in the plasma ionized calcium level, which can have a local effect on the cardiac conduction system and generate life threatening arrhythmia. For this reason, the femoral vein is preferable to the subclavian or internal jugular vein to decrease the risk of arrhythmias arising from return of hypocalcemic blood close to the AV node. Although the presence of a catheter in the femoral vein limits the patients mobility, it is a safer alternative to the subclavian vein, and in many patients treated with TPE, mobility may not be possible and treatment is of short duration.

When the nature of the disease requires chronic TPE(e.g. hypercholesterlemia, cryoglobulinemia), the creation of a permanent access is preferred. Based on individual cases, patients may undergo placement of a central catheter for long-term use, such as the Broviac Hickman catheters or have an arteriovenous fistula or polytetrafluorethylene graft.

Anticoagulation

Anticoagulation is mandatory for plasmapheresis procedures whether by MPS devices or by centrifugal devices. Citrate solutions and heparin may be used in either types of devices. In general, filtration devices use heparin, whereas centrifugal machines mostly operate with citrate [12].

Heparin

Heparin sensitivity and half-life vary greatly in patients, and individual adjustments of dosage is necessary. For most patients heparin can be used at an initial loading dose of 50 U/kg, followed by an infusion rate of 1000 U/hour. Frequent monitoring (every half hour) of the activated clotting time (ACT) to maintain an ACT equal to 180 – 220 seconds is desirable (1.5 – 2.0 times normal). Heparin doses should be increased with increasing plasma filtration rates and with decreasing HCT, probably as a result of increasing volume of distribution (with decreasing HCT) and increased net removal (heparin has a sieving coefficient of one and is removed more rapidly as filtrations rates increase) [18].

Citrate

Acid-citrate dextrose (ACD) is used as the anticoagulation solution for most centrifugal plasma exchange procedures. This technique, however, can be modified for use with an MPS system [19]. ACD comes in 2 standard formulations. Formula A (ACD-A) contains 2.2 g/dL of sodium citrate and 0.73 g/dL of citric acid. Formula B (ACD – B) contains 1.32 g/dL of sodium citrate and 0.44 g/dL of citric acid. ACD – B is commonly used for Haemonetics centrifugal system, and ACD – A is used for the Cobe centrifugal and membrane (TPE) systems. Citrate solutions can be infused into the blood access at a ratio of citrate to blood of 1 : 15 – 1 : 25. Citrate chelates calcium, which is a necessary cofactor in the coagulation cascade, and this inhibits thrombus formation and platelet aggregation. The higher citrate flow ratios (1 : 10 to 1 : 15) tend to be used for the continuous centrifugal flow system (but 1 : 25 when fresh frozen plasma (FFP) is used as a replacement fluid). Lower citrate flow ratios (1 : 15 to 1 : 25) are recommended for membrane TPE.

Although bleeding disorders are not common with citrate, hypocalcemia commonly

occurs (60 – 70% of the overall complications during TPE). Therefore, hypocalcemic symptoms and signs must be carefully watched for (perioral and/or acral paresthesias, shivering, light-headedness, twitching, tremors and, rarely, continuous muscular contractions that result in involuntary carpopedal spasm). If hypocalcemia becomes more severe, symptoms can progress to frank tetany with spasm in other muscle groups, including life-threatening laryngospasm. Generalized (grand mal) seizures have been reported. These symptoms and signs may be accentuated by alkalosis due to hyperventilation. Reductions of ionized calcium also lengthen the plateau phase of myocardial depolarization – manifested electrocardiographically by prolongation of the QT interval. Very high citrate levels, with corresponding low ionized calcium lead to depressed myocardial contractility, which although very rare, can provoke fatal arrhythmias in apheresis patients.

Prevention of Hypocalcemia

The following measures have been applied for prevention of hypocalcemia during TPE:

– *Limiting the blood flow rate*. The rate of citrate infusion must not exceed the capacity of the body to metabolize citrate rapidly. The ability to metabolize citrate will vary from patient to patient. Because the amount of citrate infused will be proportional to the blood flow rate, very high blood flow rates should not be used in small patients. When ACD – A is being infused in a 1 : 10, 1 : 15, or 1 : 25 volumetric dilution with blood, the blood flow rates should not exceed 60, 100, or 150 mL/min, respectively. In smaller patients, the maximum blood flow rate is even less. The maximum recommended blood flow rate can be estimated in mL/min as a proportion of body weight depending on the ACD – A-blood ratio being used:

ACD – A-blood ratio	Maximum blood flow rate (mL/min)
1 : 10	1.2 × body weight (kg)
1 : 15	2.0 × body weight (kg)
1 : 25	3.0 × body weight (kg)

– For example, when using an ACD – A-blood dilution ratio of 1 : 15 in a 30 kg patient, the maximum recommended blood flow rate would be 2 × 30 = 60 mL/min. One of the systems, the Cobe Spectra, will estimate the patient's blood volume by a nomogram. It will then automatically set the blood flow rate to limit the rate of which citrate is being infused. Patients with liver disease may have an impaired ability to metabolize citrate, and in these patients, citrate infusion should be performed with great caution.
– *Oral ingestion of 500 mg tablets of calcium carbonate every 30 min.*
– *Reduction of the proportion of ACD – A* when FFP is the replacement fluid, because FFP contains up to 14% citrate by volume.
– *Infusion of boluses of calcium gluconate 10%* when mild symptoms of hypocalcemia are present.
– *Continuous infusion of Calcium Gluconate 10% (10 mL per L of return fluid)* [20].

It is also important to mention the danger of alkalemia in patients with previous metabolic alkalosis, since citrate is metabolized to bicar-

Table 6. Choice of Replacement Solution

Solution	*Advantages*	*Disadvantages*
Albumin	No risk of hepatitis Stored at room temperature Allergic reactions are rare No concern about ABO blood group Depletes inflammation mediators	Expensive No coagulation factors No immunoglobulins
Fresh frozen plasma	Coagulation factors Immunoglobulins "Beneficial" factors Complement	Risk of hepatitis, HIV transmission Allergic reactions Hemolytic reactions Must be thawed Must be ABO compatible Citrate load

bonate. In patients with liver disease, who may have impaired ability for citrate metabolism, this infusion should be accurately monitored, since their risk is markedly higher.

Replacement Solution

The selection of the type and amount of replacement fluids is an important consideration in the prescription of plasmapheresis. The diversity of disease and patient conditions makes the elaboration of uniform suggestions for replacement fluid difficult. Nevertheless, certain guidelines are useful, and they can be modified by the specific conditions encountered.

In most plasmapheresis procedures, replacement by colloidal agents is essential to maintain hemodynamic stability. In practice this is limited to albumin, generally in the form of 5% solution, or FFP. The advantages and disadvantages of each is outlined in Table 6. FFP has the advantage of being similar to the filtrate from the patient but is associated with side effects such as allergic reactions, hypocalcemic reactions from the citrate in the plasma and a small but measurable incidence of transmission of hepatitis B (0.0005%/unit), hepatitis C (0.03%/unit), and HIV (0.0004%/unit). Although these infection risks are now much smaller with predonation and postdonation testing, it should be kept in mind that with each treatment, patients are exposed to 3 L, equivalent to 10 – 15 U of plasma from equal number of donors. Urticaria which may be severe is frequently present with the use of FFP. Rarely, anaphylactic reactions result in a form of noncardiogenic pulmonary edema caused by passive transfusion of leukoagglutinins. However, one must remember that even the so-called advantage of FFP, i.e. its similarity to the composition of filtrate, may be viewed as a drawback, since it makes the measurement of the efficiency of the procedure (e.g. by following IgG and other immunoglobulin concentrations) difficult and re-

plenishes factors that could participate in the inflammatory process. Because FFP may contain appreciable amounts of anti-A and anti-B isoagglutinins, ABO compatibility between donor and recipient is necessary.

At present, the specific indications for the use of FFP in plasma exchange are:

– TTP/HUS
– preexisting defect in hemostasis,
– risk of cholinesterase depletion,
– when the fibrinogen level is low (< 125 mg/dL). In this situation, one should consider replacing some or part of the removed plasma with FFP.

Finally, since plasmapheresis also depletes coagulation factors, replacement by albumin and crystalloids alone may deplete these factors and place the patient at increased risk of bleeding. This is not likely to occur after 1 – 2 plasma exchanges, particularly if they are performed more than a day apart, since the half-life for most clotting factors is approximately 24 – 36 hours. Nevertheless, we recommend measurement of prothrombin time (PT) and partial thromboplastin time (PTT) before the third and subsequent procedures; if these are 1.5 times greater than control samples, at least 2 – 3 units of FFP should be infused as part of the replacement solution [12].

Albumin

Because of the above concerns with the use of FFP, our approach is to recommend the initial replacement solution to be albumin. Albumin, at a concentration of 5 g/dL, can be replaced in equivolumes to the filtrate, and with modern equipment this can be done simultaneously and at the same rate as the plasma removal. However, since a substantial proportion of the albumin that is infused early during the procedure is exchanged during the course of plasmapheresis procedure, a more economical approach is to replace the first 20 – 30% of each plasma volume with crystalloids, such as normal saline or Ringers lactate, and substitute the other two-thirds of the plasma volume with 5% albumin. This ratio would result in a final concentration of albumin in the vascular space of approximately 3.5 g/dL, sufficient to maintain oncotic pressure and avoid hypotension. Purified human serum albumin (HSA) solutions do not transmit viral diseases because of prolonged heat treatment during processing and have become a favored replacement fluid in TPE. A pitfall in the routine use of albumin is its cost and the lack of clotting factors. It has an excellent overall safety record. The incidence of adverse reactions of any kind has been estimated to be 1 in 6,600 infusions [21]. Severe, potentially life-threatening reactions occur in only about 1 of every 30,000 infusions. These reactions have been attributed to:

– antigen-antibody reactions generated by an altered albumin molecule, soluble immunoglobulin-albumin complexes that are capable of agglutinating red blood cells, presence of sodium caprylate (a protein stabilizer that can make albumin antigenic) ethylene oxide that can react with a variety of serum proteins including albumin, and IgE antibodies against ethylene oxidealbumin complexes;
– reactions due to proteins different than albumin, since the preparations are 96% purified and carry other proteins such as factor XII and IgA in a patient with IgA deficiency who could be sensitive to the Ig; and
– contamination with live bacteria and pyrogens.

In some cases, there may be a rational for using FFP as the sole replacement fluid. In particular, this applies to plasma exchange

therapy used for HUS and TTP, since there is some evidence that infusion of FFP by itself may be therapeutic and because, in the presence of thrombocytopenia in these diseases, the risk of bleeding by minor perturbations in the coagulation factors may be higher. In patients presenting with these symptoms, we use FFP as the sole replacement fluid.

In recent years, decreased availability, rising costs, recognition of drug interactions with albumin (i.e. ACE inhibitors) and a fear of disease transmission have lead several groups to reconsider the use of colloid starches as partial or full replacement for plasma exchange [22].

Starch Replacement

A 3% solution of hetastarch (HES) has been utilized for the first L of albumin replacement. This technique provides 25 – 50% of the total fluid replacement per procedure and offers a decreased risk of allergic and anaphylactoid reactions compared to albumin. Likewise, it has been estimated that a potential annual savings of $44,000 can be achieved with this strategy [22].

Six percent HES has a molecular weight of 480,000 kd, and 10% pentastarch has a molecular weight of 264,000 kd. Both are cleared by urinary excretion. Pentastarch is eliminated twice as fast as pentastarch in a 24 hour period, which makes it preferable. However, pentastarch is only licensed to use during leukapheresis and as a volume expander.

Colloid starch should be avoided in patients with renal failure, congestive heart failure, pulmonary edema, hyperviscosity, corn or starch allergy, coagulopathies and liver failure.

The amount of fluid replacement is generally dependent on the patient's volume status. These can be varied, either manually or automatically, from 100% of the removed volume to < 85%. Further reduction may be too abrupt, since it occurs initially in the vascular space and may result in hemodynamic instability [12].

Complications

The side effects observed in plasma exchange are generally not severe and can be managed easily if they are anticipated.

According to the different series, complication rates for patients vary from 4 – 25% with an average of 10% in the majority of studies [23, 24]. Minimal reactions occur in about 5%

Table 7. Complications of Plasmapheresis

– Related to vascular access
Hematoma
Pneumothorax
Retroperitoneal bleed
– Related to the procedure
Hypotension from externalization of blood in the extracorporeal circuit
Hypotension due to decreased intravascular oncotic pressure
Bleeding from reduction in plasma levels of co agulation factors
Edema formation due to decreased intravascu lar oncotic pressure
Loss of cellular elements (platelets)
Ethylene oxide-associated hypersensitivity re-actions
– Related to anticoagulation
Bleeding, especially with heparin
Hypocalcemic symptoms (with citrate)
Arrhythmias
Hypotension
Numbness and tingling of extremities
Metabolic alkalosis from citrate

Table 8. Strategies to Avoid Complications during Plasmapheresis

Complication	*Management*
Hypocalcemia	Prophylactic infusion of 10% $CaCl_2$ during treatment.
Hemorrhage	2 units of FFP at the end of the session.
Thrombocytopenia	Consider membrane plasma separation
Volume-related hypotension	Consider continuous flow separation with matched input and output.
Infection postpheresis	Infusion of intravenous immunoglobulin (100 – 400 mg/kg)
Hypokalemia	Ensure a potassium concentration of 4 mmol/L in the replacement solution
Membrane biocompatibility	Change membrane or consider centrifugal method of plasma separation.
Hypothermia	Warm replacement fluids.
ACE inhibitors	Discontinue ACE-inhibitor 24 – 48 hours before treatment.
Sensitivity to replacement fluids	Consider diagnostic evaluation (i.e ant-IgA antibody, anti-ethylene oxide antibody, anti-human serum albumin antibody, endotoxin assay, and bacterial cultures of replacement fluid, etc.). Consider starch-based fluids. Premedication regimen for sensitized individuals: 1) prednisone 50 mg orally 13 hours, 7 hours, and 1 hour pretreatment, 2) diphenhydramine 50 mg orally 1 hour pretreatment and 3) ephedrine 25 mg orally 1 hour pretreatment and before pheresis.

ACE = angiotensin converting enzyme. Modified from [24], p 822.

of cases, and are characterized by urticaria, paresthesias, nausea, dizziness and leg cramps. Moderate symptoms represent around 5 – 10%. They include hypotension, chest pain, and ventricular ectopy. All are usually brief and had no sequelae. Severe events are present in < 3% of cases and are mainly related to anaphylactoid reactions associated with FFP administration. Several investigators estimate the mortality rate between 3 – 6 per 10,000 procedures. The majority of deaths include anaphylaxis associated with FFP replacement, pulmonary embolism, and vascular perforation.

The most important complications encountered in plasma exchange are summarized in Table 7. Strategies for avoidance and management of these complications are summarized in Table 8.

Hemodynamic Complications

Hypotension has an overall incidence of 2% according to the different series reported. The Canadian Apheresis Study Group reported 120 instances of hypotension that accounted for 18% of their total number of complications [24]. Hypotension is mainly due to intravascular volume depletion which may be exaggerated by blood in the extracorporeal circuit of the cell separator, especially with centrifugal cell separators (250 – 375 mL). Other reasons include vasovagal episodes, hypooncotic fluid replacement, delayed or inadequate volume replacement, anaphylaxis, cardiac arrhythmia, and cardiovascular collapse.

Hematologic Complications

Hemorrhagic episodes are very rare. After a single plasma exchange, immediate changes constitute reduction in fibrinogen of 80%, decreased prothrombin by 60%, PTT by 100%, factor V by 58%, factor VII by 53%, factor VIII by 50%, factor IX by 43%, factor X by 68%, and Antithrombin (AT)-III by 58%. Recovery of coagulation factors is biphasic characterized by a rapid initial increase up to 4 hours postpheresis and followed by a slower increase 4 – 24 hours post exchange. Twenty-four hours after treatment, fibrinogen levels are approximately 50% and AT-III levels are 85% of initial levels; both require 48 – 72 hours for complete recovery. One day following treatment, the prothrombin level is 75% and factor X is 30% of the original level; all other coagulation factors completely recover to normal values. When multiple treatments are performed over a short period, the depletion in clotting factors is more pronounced and may require several days for spontaneous recovery. As stated before, under these conditions it is advisable to replace 2 units of FFP at the end of the treatment.

Angiotensin-Converting Enzyme (ACE) Inhibitors

Anaphylactic or atypical anaphylactoid reactions have been reported in patients undergoing hemodialysis, low-density lipoprotein affinity apheresis, and staphylococcal protein A affinity apheresis [25, 26]. These reactions have been related to negatively-charged membranes or filters. In a retrospective review over a 12-year period, 299 patients who received colloid replacement were evaluated. All patients receiving an ACE inhibitor suffered reactions. Of 285 patients not receiving ACE inhibitor therapy, 20 patients (7%) experienced flushing or hypotension. ACE inhibition was associated with 14 of the 34 reactions evaluated (41%). When patients took the ACE inhibitor within 24 hours of the treatment, reactions occur in 78% of treatments, usually within the first 15 minutes of the procedure [26]. Experimental evidence has shown that this reaction is not related to the extracorporeal circulation alone. It is speculated that the fragments of prekallikrein activating factor present in human albumin leads to endogenous bradykinin release. The severity of the reactions depends on different variables, including drug type and lot of albumin (which may contain different concentrations of the prekalikrein activating factor). Ideally, therefore, short-acting ACE inhibitors should be held 24 hours, and long-acting ACE should be held 48 hours prior to plasma exchange.

Infection

The true incidence of infection in TPE is controversial. Studies have not clearly shown a significantly higher occurrence of opportunistic infections among patients treated with immunosuppression and therapeutic plasma exchange than with immunosuppressive therapy alone. However, if a severe infection develops in the immediate post plasma exchange period, a reasonable approach would be a single infusion of immunoglobulins (100 – 400 mg/kg intravenously (IV) [24].

Electrolyte, Vitamin, and Drug Removal

– Hypokalemia: When the replacement solution is albumin, there could be a 25% reduction is serum potassium levels in the immediate postpheresis period. The

risk of hypokalemia can be reduced by adding 4 mmol of potassium to each L of replacement solution.
- Metabolic alkalosis: may result from large amounts of infused citrate.
- Vitamins: Levels of vitamin B_{12}, B_6, A, C and E diminish immediately (24 – 48%) after treatment and return to baseline values in 24 hours.
- Drugs: In general, drugs that are significantly cleared by plasma exchange are the ones that have small volumes of distribution and extensive protein binding [27]. Evidence shows that supplemental dosing of prednisone, digoxin, cyclosporine, ceftriaxone, ceftazidime, valproic acid, and phenobarbital is not necessary after plasma exchange. In contrast, the dosages of salicylates, azathioprine and tobramycin should be supplemented. The many reports of phenytoin clearance are conflicting, thus it is necessary to carefully monitor unbound drug levels. Therefore, we generally recommend that *all scheduled medications should be given immediately after the procedure.*

Treatment Strategies

General orders of plasmapheresis are listed in Table 9. The following sections describe plasmapheresis treatment prescriptions in selected diseases. Several excellent recent reviews have summarized the utility and efficacy of TPE in renal and non-renal diseases [17, 28, 29].

Anti-glomerular Basement Membrane (anti-GBM) Disease

Before 1975, anti-GBM nephritis was associated with very poor prognosis; 85 – 90% of

Table 9. General Orders for Plasmapheresis

- Calculate the plasma volume
- Measure the preplasmaperesis PT, PTT and platelet count.
- When feasible, measure the plasma level of the substance targeted for removal. (e.g. anti-GBM antibody titer, acetylcholine-receptor antibody, cryoglobulin).
- Space treatments approximately 24 hours apart (variable).
- For heparin anticoagulation (low bleeding-risk patient): Heparin 50 U/kg initially, then 1000 U/hour. Target ACT (when baseline mean control value = 145 seconds) during the procedure is about 180 – 220 seconds. If the ACT is < 3 minutes, increase the fusion rate by 500 U/hour. If the ACT is > 4 minutes, discontinue heparin infusion, continue to measure the ACT, and resume heparin infusion at a reduced rate as appropriate. Stop heparin infusion about 30 minutes prior to the end of the procedure.
- For citrate anticoagulation, use ACD-A at 1 : 15 to 1 : 25 dilution with blood.
- Use calcium infusion if necessary.
- Cardiac monitor
- Administer scheduled medications only at the end of the session*.
- Catheter care as per routine.

*Especially cyclophosphamide and azathioprine. Prednisone and prednisolone are minimally removed by TPE and supplemental dosing after TPE has been found to be unnecessary.

patients treated with various combinations of steroids and cytotoxic drugs progressed to ESRD or death within 5 years of diagnosis. Two studies [30, 31], although small, suggested a beneficial effect of plasma exchange as an adjunct to conventional immunosuppressive therapy in anti-GBM disease, as evidence by more rapid declining anti-GBM antibody titers, lower mean serum creatinine levels at end of therapy, and fewer patients progressing to renal failure. The largest published series of > 59 patients treated at Hammersmith Hospital, suggest that significant recovery of renal function was infrequent in patients who were oliguric, had a serum creatine value above 6.8 mg/dL, or required dialysis at presentation, even though anti-GBM antibody titers were reduced significantly. For these reasons, in patients with severe disease [oliguria, dialysis, serum creatinin value > 600μmol/L (6.8 mg/dL)], plasmapheresis should probably be reserved for treatment of pulmonary hemorrhage because renal function is unlikely to recover even with aggressive treatment.

The frequency of plasmapheresis should be high enough to rapidly decrease the circulating level and an exchange of 2 plasma volumes daily for 7 consecutive days is indicated in this disease. Because of the consequences of even small titers of circulating antibody, our practice is to continue plasmapheresis for a second week on an alternate-day basis, to allow the cytotoxic effects of immunosuppressive medicines to become evident. Note that diagnosis or follow-up study of the disease by measurement of circulating anti-GBM antibody may be positive in only 65 – 70% of cases. A renal biopsy is often indicated for definitive diagnosis of any rapidly progressive renal failure. However, if the index of suspicion for the presence of the anti-GBM disease is high and the clinical situation is suggestive (rapidly rising creatinine, lung hemorrhage) and because of the time needed for renal biopsy and the need to be cautious about plasmapheresis for 24 hours after biopsy to reduce the risk of bleeding, our recommendation is to initiate plasmapheresis of large plasma volumes (2 plasma volumes each day) for 2 days before biopsy and defer biopsy to a time when the level of circulating antibodies is low. Citrate anticoagulation may be particularly indicated in this case to decrease the risk of pulmonary or renal bleeding. Plasmapheresis beyond a second week may be necessary, and both clinical course as well as anti-GBM antibody titers (if available) will dictate such a need.

Equal volumes of removed plasma are replaced with 5% albumin. If patient is in fluid overload, reduce the amount of albumin solution infused to 85% (but not less) of the removed plasma volume.

Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

TTP is a syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever, and renal dysfunction. Although there has been varied treatment success with corticosteroids, antiplatelet agents and splenectomy, there is currently general agreement that plasma exchange with replacement with FFP or cryosupernatant is the treatment of choice [33 – 38]. Prior to the use of TPE, mortality with TTP was as high as 90%.

The recommended regimen is 1.5 PV for the first 3-treatments followed by one plasma volume exchange thereafter. The procedure is performed daily until the platelet count is normalized and hemolysis has largely ceased (as evidenced by LDH level below 400). Se-

rum creatinine and urine output have a delayed recovery, and generally improve after resolution of thrombocytopenia. Usually 7 – 10 treatments are required to induce remission. Relapse may occur in 50% of patients within a few days of stopping treatment, so it is advised not to remove the vascular access catheter until the platelet count is at least 100,000/mm^3 for 5 days without treatment. If platelet count decreases to < 100,000/mm^3, one can resume plasmapheresis on every-other-day schedule for 5 more treatments. It should be emphasized also that citrate in FFP may exacerbate hypocalcemic symptoms.

In children, HUS is frequently a benign illness that often responds to supportive therapy. Although plasmapheresis is effective in shortening the duration of the illness, the difficulties of plasmapheresis in children outweigh the benefit in most cases. However, there may be a role of plasmapheresis in pediatric cases where supportive therapy does not reverse a rapidly deteriorating clinical condition [37].

Considering the severe prognosis (maternal and fetal) of TTP in pregnancy and the clear benefit in non-pregnant patients, TPE is also the treatment of choice for TTP during pregnancy despite the possibility of treatment-induced removal of pregnancy maintaining hormones [38].

Except for mitomycin-induced TTP and cancer-associated HUS, in which plasma perfusion over protein A column has been found to be more effective than the conventional exchange, the general recommendation is the use of standard plasma exchange for secondary causes of TTP-HUS.

Cryoglobulinemia

Plasma exchange has been used for 20 years for the treatment of cryoglobulinemia. Although there are no randomized controlled studies to document the efficacy of plasmapheresis in the disease, almost all the published reports demonstrate the efficacy of plasmapheresis if the patient has overt symptoms or has progressive renal failure [39 – 42]. Indications for TPE include:

- thrombocytopenia (platelet count < 50,000/mm^3) or petichiae, or both;
- hyperviscosity syndrome;
- cryoglobulin titer > 1%;
- patient about to undergo surgery requiring hypothermia; and
- renal insufficiency.

In general, patients are treated with immunosuppression and plasma exchange, but some investigators are concerned that this approach may have detrimental effects when there is association with viral hepatitis C.

A suggested prescription is to exchange one plasma volume thrice weekly for 2 – 3 weeks. The replacement fluid can be 5% albumin, which must be warmed to prevent precipitation of circulating cryoglobulins. IgM antibodies may reaccumulate rapidly and may require chronic treatment once a week.

Selective removal techniques can be used to eliminate or minimize the need for replacement fluid. Double cascade filtration, which allows the separation of cryoglobulins (based on the high molecular weight) is a new technique which can substantially eliminate the need for replacement fluid, yet it is time consuming, more expensive, prone to clotting and increasingly difficult to obtain in the United States. Cryofiltration is another method that selectively removes cryoglobulins with a special filter by cooling plasma in an extracorporeal system, after which plasma is reincubated and can be reinfused to the patient [42].

Pauci-immune Rapidly Progressive (Necrotizing) Glomerulonephritis

Patients with this entity usually have either Wegener's granulomatosis, polyarteritis nodosa or "renal-limited" disease. Many patients have anti-neutrophil cytoplasmic antibodies (ANCA) in their circulation. In some studies ANCA titers correlate with disease activity, and ANCA seem to contribute to the pathophysiology of pauci-immune rapidly progressive glomerulonephritis (RPGN) through reactivity with neutrophils, endothelial cells, and other inflammatory mechanisms. Available data indicates that 80% of these patients progress to ESRD without therapy with high dose immunosuppression or cytotoxic drugs. The results of 5 randomized trials argue against a role for plasma exchange in mild forms of pauci-immune RPGN [43 – 47]. Pusey et al., however, in a randomized trial on 48 patients showed a potential benefit when plasma exchange was used as an adjunct to conventional immunosuppressive therapy in patients who were originally dialysis dependent [45]. These results probably reflect the efficacy of immunosuppression in controlling the inflammatory response and preservation of renal function.

Plasma exchange should be at least daily for 4 days for the first week, using 4-L exchanges with albumin and FFP to avoid coagulopathy. Response to therapy should be monitored with repeated assessments of urine output, serum creatinine values and possibly ANCA titers. For those patients with positive ANCA, there is a subpopulation with IgM ANCA who might be at a particular risk for pulmonary hemorrhage. If these antibodies are pathogenic, then a centrifugal method of plasma exchange may be required, since standard membrane plasma separation may be relatively inefficient in removing the large IgM-containing immune complexes.

Multiple Myeloma and Paraproteinemias

Renal failure complicates 3 – 9% of cases of multiple myeloma and is associated with poor prognosis. Renal impairment is caused by toxicity of myeloma light chains to renal tubules, although other factors can also contribute, including hypercalcemia, hyperuricemia, cryoglobulinemia, amyloidosis, light chain deposition, hyperviscosity, infections, and chemotherapeutic agents. Response to chemotherapy is the major factor that conditions patient survival. Individuals with tumors unresponsive to chemotherapy have a poor prognosis regardless of the regimen employed. Serum levels of light chains and severity of renal damage are the main factors for the recovery of renal function.

Two randomized controlled trials of TPE in multiple myeloma have been reported [48, 49]. In a trial of 29 patients with mean pretreatment serum creatinine levels of 11 mg/dL, 13 of 15 patients treated with TPE (3 – 4 L of plasma exchange on 5 consecutive days) had substantial return of renal function (to a mean creatinine of 2.6 mg/dL) within 2 months, whereas improvement occurred in only 2 of 14 patients treated without TPE.

Well-established renal failure considered to be due to cast nephropathy may respond less dramatically, but a combination of TPE and chemotherapy has been successful if treatment is initiated prior to the onset of oligoanuria. Johnson et al. recommend the use of biopsy to determine the density of cast formation as a guide to the eventual response to TPE. If renal biopsy is performed and TPE initiated soon after, there is a potential risk of postbiopsy bleeding from pheresis-induced

removal of coagulation factors; therefore, partial replacement with FFP is recommended in order to attenuate the coagulopathy.

If chemotherapy is successful in limiting new light chain synthesis, then a single prescription of 5 consecutive plasma exchanges may be sufficient to control the deleterious effects of light chains. Further treatments may be necessary if there is continued light chain production. Having identified a given abnormal "spike" as a light chain by immunofixation, regular monitoring by serum protein electrophoresis is an easy means to detect recurrent light chain accumulation.

Lupus Nephritis

Several prospective randomized controlled trials do not support a role for plasma exchange in the routine treatment of lupus nephritis [50 – 54]. There is experimental and clinical evidence that rapid removal of circulating antibody by plasma exchange triggers a rebound B-cell clonal proliferation and enhanced antibody synthesis. Because proliferating cells have increased vulnerability to cytotoxic agents, it has been suggested that plasma exchange may be useful in patients with lupus nephritis if synchronized with pulse cyclophosphamide (the latter administered shortly after plasma exchange).

An international trial has been designed to take advantage of this proposed mechanism [55]. Over 170 patients enrolled from 35 centers in Europe, Canada and the U.S. Partial reporting from the study center in Germany has described a rapid beneficial response in all 14 patients undergoing the synchronized protocol with 8 remaining off all therapy for a mean of 5.6 years. Unfortunately 4 of 14 patients developed irreversible amenorrhea and one patient developed a squamous cell carcinoma of the oropharynx within 17 months of treatment initiation. Definitive results are pending.

Lupus Anticoagulant and Anti-phospholipid Syndrome

Considering that the lupus anticoagulant is either an IgG, IgA or IgM antibody which binds to platelet phospholipid and, by cross reactivity, to cardiolipin, it is not surprising that plasma exchange has been used to treat this disorder. Initial studies report sporadic cases of successful reduction of antibodies in patients with lupus anticoagulant and microangiopathy. Frampton et al. [56] performed repeated exchanges approximating 3 – 4 treatments per week starting from the 14th week of pregnancy until successful delivery after 34 weeks, while Fulcher et al. [57] performed a total of 6 exchanges beginning at the 24th week followed by successful cesarean section on week 29. In both of these studies there was a substantial lowering of the offending antibody following apheresis.

The prescription would need to be given on an individual basis, however a reasonable schedule is 3 – 5 treatments over a 7 day period. Patients must be monitored by specific antibody testing, since PTT values will be invalid after plasma exchange is initiated.

IgA Nephropathy

IgA nephropathy is the most common form of glomerulonephritis. Originally considered to be relatively benign, prolonged follow up suggests that 30 – 35% of patients will progress to ESRD. The majority of patients will have a relatively indolent course, but about

10% will present with a rapidly progressive glomerulonephritis with exuberant crescent formation and an accelerated decline to ESRD. The removal of circulating IgA complexes by plasma exchange would appear to be an appealing therapeutic approach. In one series, Hene and Kater [58] report a substantial decline in serum creatinine in 2 patients presenting with rapidly progressive disease in which plasma exchange was used without steroids or any other immunosuppressive treatment. This finding is confirmed by various other reports in which were treated in the same way [59]. Thus, although, there is no controlled studies, the available data suggest a possible beneficial effect of TPE in the treatment of IgA-associated RPGN.

Focal Segmental Glomerulosclerosis (FSGS): Recurrence Post-transplant

FSGS has an estimated recurrence of 15 – 55% with a rapid onset of proteinuria after renal transplantation. A protein which has a molecular weight < 100,000 daltons, which is capable of increasing glomerular permeability to albumin has been characterized in these patients [60]. A recent report in which standard plasma exchange (1.5 plasma volumes with 5% albumin as replacement fluid for 3 consecutive days, then every other day up to a total of 9 treatments) was performed in patients soon after the recurrence of proteinuria reduced protein excretion from 11.5 to 0.8 g/day in 6 out of 9 patients [61]. Based on these results, the authors concluded that plasma exchange is likely to be effective in the treatment of recurrent FSGS if treatment is initiated promptly after the initiation of proteinuria and there is no significant hyalinosis in the allograft biopsy.

Transplant Candidate with Cytotoxic Antibodies

For patients with a high level of cytotoxic antibodies, HLA class I, who are in risk of hyperacute rejection, plasma exchange using protein A columns for the immunoadsorption has been used as an alternative to significantly reduce the PRA levels [62 – 64]. Hakim et al. showed a reduction of 40% in the antibody levels after 8 plasma volumes processed by immunoadsorption, however antibodies returned toward pretreatment levels after 4 weeks [63]. Therefore, this approach is not recommended as a routine clinical practice.

Non-renal Indications of Therapeutic Plasma Exchange

Acute Guillain-Barré Syndrome (GBS)

This entity appears to be mediated by a monophasic IgM, anti-peripheral nerve-myelin antibody, and a high titer IgG anti-ganglioside antibodies. The IgM antibody can be removed very efficiently by plasma exchange or inhibited by IV gammaglobulin early in the course of the disorder. With plasma exchange the level is reduced to < 20% by 2 – 3 weeks, whereas without plasma exchange levels do not decrease to 20% for 3 – 9 weeks. In the U.S., IV gammaglobulin is generally reserved for situations in which plasma exchange is not available or cannot be done for several days.

The most compelling evidence for the efficacy of TPE comes from a multicenter trial involving 21 medical centers coordinated by

Johns Hopkins University [65]. This study randomized 245 patients to be treated with either supportive therapy or plasma exchange. Those receiving TPE had a substantially shortened duration of motor weakness (40 vs. 29 days) and required shorter period of ventilatory support (48 vs. 24 days).

The GBS Study Group [65] found 4 factors correlating with poorer outcomes including

- old age,
- time of onset of disease of 7 days or less,
- need for ventilatory support, and
- a decreased mean amplitude of ≤ 20% of normal of the compound muscle action potential after a distal stimulus. Delay in treatment may result in severe dysfunction, requiring twice as many months for recovery.

Early and accurate diagnosis is crucial. Hospitalization is mandatory since the progression is unpredictable. Respiratory function (including tidal volume, negative inspiratory force, vital capacity, and oxygen saturation) and physical activity should be monitored. Should the patient become unable to walk unaided, demonstrate significant respiratory impairment, or develop bulbar insufficiency (marked by loss of ability to gag or swallow) TPE should be initiated promptly. Usually one to 1.5 plasma volumes should be started within 12 – 24 hours of the decision to perform TPE, and should be performed daily for the first 5 days, then 5 more single-plasma volume exchanges every other day. Five percent albumin is the recommended replacement solution. FFP has also been used, and in at least one study, did demonstrate partially superior benefit compared to albumin. However, results from the French prospective, double-blind, randomized multicenter trial found that FFP was associated with more adverse incidents than albumin and recommended that FFP be abandoned as replacement solution in GBS [66]. Some also suggest the IV infusion of IgG (40 g) at the end of the treatment.

The Dutch study concluding that IV gammaglobulin treatment for acute GBS is at least as effective as plasma exchange and may be superior needs independent confirmation [67]. An accompanying review found these results difficult to interpret because the patients treated with TPE did less well than expected [68]. A recent comparison of IV immunoglobulins and plasma exchange for neurologic diseases suggested that those receiving IV immunoglobulins may have a tendency to relapse [69].

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is believed to be an autoimmune disease characterized by a progressive or relapsing course, of symmetric motor and/or sensory deficits and absence of systemic symptoms. Diagnostic criteria vary somewhat across institutions and investigators, but the following criteria are used most often:

- disease present > 2 months (distinguishing it from acute disease, GBS), and of a steadily progressive, monophasic, or relapsing course;
- symmetrical proximal and distal motor and sensory loss usually with hyperreflexia; and,
- elevated cerebrospinal fluid (CSF) protein (generally > 0.4 g/L), with < 10×10^6/L cells.

Electrophysiologic studies generally reveal slowed nerve conduction in motor and afferent fibers, consistent with a demyelinating process. The etiology of CIDP is not known, but an autoimmune disorder is suggested by

the inflammatory cell infiltrate typically seen in affected nerves.

In 1986 Dyck et al. [70] reported on a controlled trial of plasma exchange vs. sham plasma exchange in 29 patients, who also received immunosupression during the study period. The TPE group had significantly better nerve conduction indices, motor and sensory function, and motor amplitude at 3 weeks. In those patients who responded, improvements generally began to fade within 10 – 14 days after treatment was discontinued, suggesting that a maintenance treatment schedule may be required to sustain remission. Indeed, a report by Feasby et al. [71] suggests that maintenance of neurologic improvement require weekly to every 3 weeks TPE for up to 6 months.

Most recently, several reports on the efficacy of FFP and immunoglobulins have appeared, with reported response rates from 60 – 100%. However, there is no comparative trial of plasma exchange and IV immunoglobulin. Until that question is resolved, it is reasonable to perform TPE in those patients who fail steroids or who have a severe clinical evolution.

The recommended regimen is 1 – 3 procedures of about 1 plasma volume per week. Improvement is usually rapid, and treatment should be continued to tailor the symptomatology of individual cases. Replacement fluids should be 5% albumin and crystalloid. FFP should not be utilized to avoid providing IgG.

Eaton-Lambert Syndrome

This is a myasthenic-like syndrome that can be idiopathic or cancer related. The syndrome is believed to be the result of an antibody-mediated blockage of acetylcholine release by the presynaptic nerve terminal, a disorder of the motor nerve terminal manifested by fatigue, proximal muscle weakness and autonomic dysfunction. The use of plasma exchange in conjunction with azathioprine and prednisone is now an accepted [72] standard therapy, along with treatment of the underlying tumor. It should be pointed out that complete remission of Eaton-Lambert syndrome is unusual with any treatment, and that slow and occasionally transient improvement is the rule. This is in contrast to myasthenia gravis, where very prompt reversal of symptoms with plasma exchange is often seen, and where prolonged and complete remissions can be induced.

The prescription consist of at least one plasma volume, 3 – 5 procedures weekly for at least 2 weeks. Replacement solutions should be crystalloid or colloid.

Myasthenia Gravis

This is an autoimmune disease, with anti-acetylcholine receptor antibodies (anti-AchR). Several uncontrolled trials [73 – 76] suggest that TPE can induce short-term improvement and numerous anecdotal reports describe dramatic post-treatment results, but there has never been a controlled trial of TPE. Nonetheless, the 1985 NIH panel concluded that TPE can be useful in certain situations [5]. The indication for plasma exchange are generally felt to include:

– disease unresponsive to conventional (i.e., cholinergic and immunosuppressive) therapy;
– episodes of acute deterioration ("myasthenic crisis");
– pre- and post-thymectomy, where TPE has been shown to diminish the period of ventilator support post-surgery; and
– during the introduction of corticosteroid therapy, when nearly 50% of patients experience a clinical deterioration.

A reasonable initial treatment prescription is 4 – 8 plasma exchanges over a 1 – 2 week period. Each treatment should equal one plasma volume, which can be replaced with albumin 5%. If the patient is in the immediate prethymectomy period, a partial replacement of approximately 1 L of FFP, given towards the end of the treatment, should help reverse the expected depletion coagulopathy. Although levels of AchR antibody are unlikely to be immediately available to monitor therapy, retrospective comparison between observed and expected declines in AchR antibodies reveal an excellent correlation with calculated total IgG removal kinetics. In seriously ill patients, daily or every other day therapeutic plasma exchange treatments are indicated.

Improvement is generally seen in 2 – 4 days, but maximal benefit may not occur for several weeks after cessation of plasma exchange. Long-term remissions are not seen with TPE, and concurrent drug therapy is necessary before and after exchange therapy. Chronic TPE (every 4 – 12 weeks) has been successfully utilized in a minority of patients.

Paraprotein-associated Polyneuropathy

Peripheral neuropathy has been found to occur in many disorders associated with the production of a monoclonal protein. These include primary amyloidosis, multiple myeloma, Waldenstrom macroglobulinemia, lymphoma, leukemia, the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin hyperpigmentation) and monoclonal gammopathy of undetermined significance (MGUS). The mechanism of peripheral nerve injury is complex, incompletely understood, and varies among the above entities. It is characterized by a mixed sensorimotor neuropathy with distal weakness, tremor, ataxia and loss of proprioception. In most patients, the antibody is IgM, but IgA- and IgG-associated neuropathies also have been described. The neuropathy seems to be associated with the binding of the antibody to certain constituents of peripheral myelin, such as myelin-associated glycoprotein or glycolipids.

In a randomized, sham controlled trial of patients with MGUS-related neuropathies, patients receiving TPE had significantly improved neurologic disability scores and muscle action potentials when compared to the sham-treated patients [77]. Sham-treated patients who were subsequently treated with TPE showed similar improvement. Those patients with IgA- or IgG-related neuropathies received the greatest benefit. Treatment prescription was 2 plasma exchange treatments per week for 3 weeks. Each exchange averaged 47 mL/kg or approximately 3.5 L of plasma volume. Replacement was with 5% albumin.

Multiple Sclerosis

Based on the analysis of various studies [78, 79], TPE in combination with immunosupressive drug therapy may be an effective therapy for MS in certain circumstances, both for chronic progressive and acute relapsing forms. Plasma exchange appears best utilized in the following settings.

In acute relapsing MS when:

– conventional corticotropin or corticosteroid therapy is ineffective,
– the attack is particularly severe, or
– conventional therapy is contraindicated. (e.g. diabetes, hypertension, pregnancy, peptic ulcer disease).

In chronic progressive MS when:

– conventional therapy has failed to either improve or stop the progression of disease,
– conventional therapy is contraindicated.

The recommended regimen has generally been between 1.0 – 1.5 plasma volumes using 5% albumin solution and crystalloid as replacement fluid. In the acute forms, 3 exchanges per week for 2 weeks, followed by a short course of maintenance weekly for 6 weeks is recommended.

Hyperviscosity Syndrome

It occurs most commonly with Waldenstrom's macroglobulinemia (50% of the time) and occasionally with myeloma (2% of the time) and cryoglobulinemia. Rarely do other causes of elevated serum proteins such as benign monoclonal gammopathy and rheumatoid arthritis cause hyperviscosity. It is produced by very high plasma concentrations of monoclonal immunoglobulins which increase red blood cell aggregation and impede overall blood flow, leading to ischemia and dysfunction of all organ systems. Usually symptoms do not occur until plasma viscosity is 3 – 4 times that of water. The clinical syndrome includes neurologic symptoms, a bleeding diathesis due to effects of the protein on platelets and clotting factors, retinopathy with dilatation and segmentation of retinal and conjunctival vessels, retinal hemorrhages, and papilledema and hypervolemia, distention of peripheral blood vessels, increased vascular resistance, and congestive heart failure. The therapeutic approach is to reduce or return the plasma viscosity to normal and reverse the neurologic symptoms, stop the bleeding diathesis, reverse or stop the visual impairment, and reverse the cardiovascular effects including hypervolemia and increased vascular resistance. TPE is universally accepted as effective treatment for acute symptomatology and can yield dramatic results, including reversal of coma [4, 80, 81]. The treatment includes plasma exchange as well as the treatment of the primary disorder. The suggested TPE regimen include single PV sessions for 2 days, to be continued 5 days if serum IgM levels are still above normal.

Idiopathic Thrombocytopenic Purpura (ITP)

ITP results from the presence of autoantibody to platelets. The antibody is usually IgG directed against membrane glycoprotein antigens. Traditional therapy includes steroids, splenectomy, immunosupressive agents, vinca alkaloids, danazol and IV immunoglobulin. Several reports describing the use of TPE have documented a rapid short-lived increase in platelet counts felt to be related to a concomitant decline in anti-platelet antibodies [82, 83]. However, TPE needs to be combined with another therapy to produce sustained remission, especially in those patients with chronic ITP. FFP is the suggested replacement solution, and it may prevent the risk of hemorrhage that these patients have. In cases of refractory ITP, staphylococcal protein A immunoadsorbent column is capable of selective adsorption of 3 subclasses of IgG and may be particularly selective for immune complexes [84, 85]. The efficacy of this approach may be in the removal of immune complexes, infusion of anaphylatoxin-producing substances such as activated complement, and stimulation of antiidiotypic antibodies, since it only removes 10% of protein compared to the regular plasma exchange.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia is characterized by the presence of autoantibodies, either cold agglutinins, which are usually IgM against the I/I antigens, or IgG (warm agglutinins) with specificity for a structure in the Rh complex that is common to all Rh types. It is usually idiopathic, but it could be associated with infection, a lymphoproliferative disorder or collagen vascular disease.

TPE has been employed for cold and warm agglutinin hemolytic anemia [86, 87]. However, many reported cases also have utilized corticosteroids and other immunosuppressive agents, and results are difficult to evaluate. From the data published to date, TPE seems to be more effective in cold agglutinin hemolytic anemia. TPE is a definite indication in cases of severe hemolysis and hemolytic anemia unresponsive to conventional drugs. Favorable results have been obtained with exchanges of 1 – 1.5 plasma volumes carried out 3 – 5 times per week using 5% human serum albumin as the plasma replacement fluid. Special attention should be paid to prevention of extracorporeal blood cooling in treatment of cold agglutinin disease.

Rh Disease

With the Rh immunization and technical advances in umbilical cord sampling and intrauterine transfusion, Rh hemolytic disease is very uncommon these days. Several reports suggest that intensive plasma exchange using up to 20 L per week can successfully lower the level of maternal antibodies directed against fetal blood antigens [88, 89]. TPE is used for situations in which the mother has been immunized against a blood antigen for which the father is homozygous and in which the mother has had a previous history of hydrops at or before 24 – 26 weeks of pregnancy. Plasma exchange should start at 10 – 12 weeks of gestation, when maternal-fetal transfer of IgG is beginning. Amniocentesis or fetal sampling is recommended at 18 – 22 weeks.

Coagulation Factor Inhibitors

The presence of coagulation factor inhibitors generate a de novo appearance of a bleeding disorder. They are usually IgG antibodies that bind to a component of the coagulation cascade, the most common being those with activity against factor VIII.

Therapy is directed to control bleeding episodes and to suppress synthesis of the inhibitory antibody. The use of large doses of factor VIII , occasionally preactivated, is the best option for these patients. However this treatment is costly, reaching up to $ 20,000 per day. Immunosuppressive agents have been used to control these antibodies together with TPE [90]. The recommended regimen varies from 2 exchanges in a 3 week period to 2 – 3 plasma volumes for 14 days. Replacement should be made with FFP to prevent dilutional coagulopathy.

Recently, plasma exchange using a staphylococcal column that removes IgG has been successfully utilized in association with prednisone and cytoxan.

Sickle Cell Anemia

Use of red cell exchange is indicated in the current management of sickle cell disease and related hemoglobinopathies. It should be carried out urgently in patients with severe infarctive crises and in many patients who are to undergo general anesthesia. Long-term prophylactic exchange or transfusion programs are recommended following strokes

and for some patients with frequent pain crises. A rigorous goal would be to maintain hemoglobin A > 50% and HCT > 30%, although some patients may not require this much. It remains controversial whether prophylactic transfusion or exchange during pregnancy is justified.

Hypercholesterolemia

TPE is a well defined indication for patients with homozygous familial hypercholesterolemia, and also for the secondary prevention of hypercholesterolemic patients suffering from pronounced coronary artery disease [91 – 94]. Ideally, elevated low-density lipoprotein (LDL) cholesterol and/or lipoprotein (Lp) a levels should be the only or at least the major risk factor, and mean interapheresis target levels of < 100 – 120 mg/dL of LDL cholesterol should be achieved. Most patients can be treated satisfactorily by weekly or biweekly processing of one patient plasma volume, however those with homozygous familial hypercholesterolemia need to be followed with post-treatment levels. Primary biliary cirrhosis can also result in severe hypercholesterolemia that leads to xantomathous neuropathy. Repeated treatments (daily for 5 days and then weekly to maintain levels) provoke resolution of xanthomas and remission of neuropathic pain, and relief of the intractable pruritus seen in these patients. It is important to say that TPE is indicated when all conservative measures, such as physical exercise, low cholesterol diet, and drug-reducing cholesterol drugs have been unsuccessful to treat the disorder.

Currently there are 5 different lipid apheresis procedures for clinical application: unselective plasma exchange, semiselective double filtration, and highly-selective immunoadsorption, chemoadsorption onto dextran sulfate, and heparin-induced extracorporeal low-density lipoprotein precipitation, the so-called HELP system [95 – 98]. The most impressive success with these treatments is the recent report demonstrating atherosclerotic regression with drugs and the dextran sulfate system [99]. TPE has lost popularity in the last few years, due to the removal of HDL and immunoglobulins, and occasional anaphylactoid reactions to replacement solutions. Today most centers prefer immunoadsorption, which uses a sepharose column of immobilized antibodies to apolipoprotein B which interacts with patients apolipoprotein B and removes the LDL cholesterol. With this method the HDL is recovered.

Recently, a new Lp a column was described based on immobilized anti-apo (a) antibodies. This column might be advantageous if Lp a is the only risk factor for a specific patient. Another device is the LDL hemoperfusor, which adsorbs LDL directly from whole blood and currently is being investigated. Preliminary reports in vitro, ex-vivo and a pilot study in 12 patients have demonstrated good efficacy and selectivity, as well as an excellent biocompatibility of the system.

Fulminant Systemic Meningococcemia

Fulminant systemic meningococcemia is an entity that when severe has a mortality rate > 70%. Large molecular weight endotoxins are considered the trigger for the release of a series of cytokines, nitric oxide (NO) and activation of monocyte-derived tissue thromboplastin, felt to be a cause of the disseminated intravascular coagulation which is often the hallmark of this disease.

Although there are no randomized, controlled trials demonstrating the benefits of TPE for fulminant meningococcemia, it should be

considered that this is often a desperate illness affecting previously healthy children and young adults in which particularly high levels of endotoxin and inflammatory mediators correlate with an unfavorable outcome. Furthermore, the weight of the available evidence is invariably in favor of this approach [100 – 103].

There are several reports using TPE with success rates up to 80% improved from a predicted 60%, and although they are not randomized trials, the weight of the present data indicates that this is a reasonable approach. The prescription is usually 30 – 40 mL/kg of plasma exchange replaced with FFP, performed as soon as the patient is diagnosed and repeated after 12 hours and the following 48 hours if the patient's condition remains critical. Delay of > 40 hours in initiating TPE is associated with a negative outcome.

New Techniques

Cryofiltration

Cryoglobulins removed by conventional cell separators quickly plug membranes due to a small pore size (0.2 um). Recently, a technique that uses a cryoglobulin filter with an average pore size of 4.3 μm have proven efficacy for the removal of cryoglobulins [42].

Blood and plasma circuits are primed with heparin and normal saline. After passing through the cell separator, plasma is continuously cooled by passing it through heat exchange tubing placed inside a refrigeration unit at 4° C (Daido Hoxan Inc., Piscataway, NJ). Cryoglobulins are selectively filtered from plasma by the high capacity cryofilter also kept at 4° C. The plasma is then rewarmed back to the patient's body temperature before being recombined with the packed red cell fraction. Pressure of the cryofilter is monitored throughout the procedure, and treatment is stopped when pressure reaches 300 – 400 mmHg. The replacement solution is 5% albumin.

HELP (Heparin Induced Extracorporeal LDL Precipitation) Apheresis

HELP system uses a fluid phase reaction of the polyanion heparin with positively-charged species such as LDL- and very low density lipoprotein (VLDL)-derived apo B, Lp(a), and fibrinogen [91, 104]. The use of a low pH buffer increases the number of positive charges on the target proteins and thus facilitates the precipitation. The resulting co-precipitate of these risk factors with heparin is then filtered off and excess heparin is removed in a special absorber containing diethylaminoethyl (DEAE) cellulose. The risk factor-depleted plasma is then subjected to dialysis in order to restore physiological pH, volume, and electrolyte conditions. On theoretical grounds, this triple risk factor removal might be and advantage of the HELP procedure. On the other hand, fibrinogen removal can be limiting in patients with poor coagulation or at risk of bleeding. Although rarely a clinical problem, risk factor removal is limited by the capacity of the precipitate filter. Because the HELP system uses a dialyzer for plasma regeneration, a modification in terms of a simultaneous HELP/hemodialysis procedure has also been developed for the treatment of patients with chronic renal failure (CRF) and LDL-induced coronary heart disease. Several non-controlled studies establish that this method has the highest grade of efficacy [105].

Thermofiltration

Initially described by Nose et al. at the Cleveland Clinic, in this technique the temperature-dependent filtration differences of different plasma components are utilized to improve the differential fractionation of LDL from HDL. During regular TPE, it was noted that temperature changes in the line systems would affect the filtration process, due to the formation of a cryogel that occluded the membrane pores. Therefore, a technique that uses plasma warming was developed, and it was found that in the temperature range between 37 – 42° C the amount of LDL cholesterol removed was the largest, whereas the HDL removed was < 0.1 g. This technique is considered safe, simple and cost-effective as compared with other extracorporeal methods. However, one limitation to its use is the requirement of heating of the plasma after its separation. Several reports have established successful reduction of cholesterol, even better than plasma adsorption, with the advantage of retaining albumin and HDL cholesterol [106].

Extracorporeal Photopheresis (ECP)

This therapy involves the extracorporeal treatment of a particular subset of cells with psoralen and ultraviolet A (PUVA). It provides marked selectivity in treating the diseased cells only. Phototherapy was popularized by Finsen in 1903, when he initiated the use of carbon arc illumination for the treatment of lupus vulgaris. Psoralens are derived from the plant *Psoralea corylifolia*. At the cellular level, psoralen binds to the pyrimidine bases of DNA. Upon exposure to UVA light, the psoralen forms covalent bonds with the DNA. The photoadduct formed disrupts DNA replication and the viability of the affected cell, but the exact mechanism of action is unknown.

Photopheresis treatments are accomplished using the UVAR photopheresis system [107]. One and a half hours after the patient receives 0.7 mg/kg of 8-MOP (8-methoxypsoralen) or 0.5 mg/kg of oxsoralen ultra, access through a peripheral vein is obtained and patients undergo a discontinuous leukapheresis procedure with exposure of removed leukocytes to ultraviolet A radiation. During the procedure, approximately 240 mL of leukocyte-enriched blood is mixed with 300 mL of the patient's plasma and 200 mL of sterile normal saline plus approximately 10,000 units of heparin. The final buffy coat preparation contains an estimated 25 – 50% of the total peripheral blood mononuclear cell compartment and has a HCT from 2.5 – 7%. The buffy coat is then passed as a 1 mm film through a sterile cassette surrounded by UVA-emitting bulbs, permitting a 180 minute exposure to UVA light, yielding an average exposure per lymphocyte of 2 Joules/cm^2. Following exposure of the cells to UVA, the buffy coat is returned to the patient. The entire procedure requires approximately 3 – 5 hours. Recommended levels of psoralen during treatment are 100 ng/mL or > 50 ng/mL within the photopheresis buffy coat bag. Substantial intra-individual variation in psoralen absorption can occur depending upon gastric contents and disease state. Thus, measurements are taken several times annually to assure the maintenance of therapeutic levels of 8-MOP.

Photopheresis is currently approved in the United States for the treatment of cutaneous T-cell lymphoma (CTCL). In the initial multicenter trial, patients with erythrodermic CTLC were treated for 2 consecutive days and for a total of 12 months. Highly beneficial results were obtained with few associated adverse effects. Eighty-three percent of patients

had improvement in their erythroderma with a mean time to development of a positive response within the skin of 22.4 weeks. Moreover, 9 patients (24%) experienced a 75% improvement in their skin lesions and 35% had a 50 – 75% improvement in their skin lesions. Likewise a decrease in the extent of CD4+ peripheral blood cells was also noted and related to disappearance of the malignant clone responsible for the lymphoma.

Aids-related Complex (ARC): There have been reports on small number of patients that ECP may have a role in upregulation of the immune system, which may be directly or indirectly related to the UVA-psoralen interaction in cells infected with the virus. Patients become culture negative, maintain a stable CD4:CD8 ratio and do not develop opportunistic infections. Further studies are needed to investigate this area.

Extracorporeal Immunoadsorption (ECI)

ECI is a treatment modality based on the use of special ligands to specifically remove blood components considered pathogenic for different diseases, mainly immunecomplexes and lipids [85]. The difference with TPE is that plasma, after passing through a column containing the specific ligand for the substance, is returned to the patient. Different substances have been used as ligands, with Staphylococcal Protein-A most widely used due to its ability to selectively ligate immunoglobulins. These columns also cause transient production of antibodies to combat the disease. Prosorba columns also stimulate the activity of natural killer (NK) cells, granulocytes, and macrophages. The main disadvantage is its cost and the requirement of trained personnel to set up and monitor the procedure.

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Vascular Access for Hemodialysis

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Introduction

Adequate care of hemodialysis (HD) patients is inseparable from the problems of creating and maintaining the patency of vascular access. An ideal permanent vascular access should:

- deliver an adequate blood flow rate,
- provide longevity of use, and
- have low complication rates for stenosis, thrombosis, and infection.

Delivery of optimal HD requires a well-functioning vascular access with a nominal blood flow rate of 400 mL/minute without access recirculation. Failure of access function limits the delivered dose of dialysis which in turn is one of the major determinants of survival on dialysis [1].

The autologous arteriovenous (AV) fistula introduced by Brescia and Cimino in 1966 comes closest to satisfying the requirements for delivering adequate blood flow while minimizing complications. It has the best 5-year patency rate and during this period requires much fewer interventions than other access constructions [2]. Although cuffed venous catheters have evolved into an alternative form of long-term vascular access for patients in whom a permanent AV access cannot be readily created, construction of a permanent vascular access is preferred since it permits repeated angioaccess for months to years while minimizing risks from infection.

Although the autologous AV fistula is the desired access for patients initiating HD, there is disproportionate use of prosthetic access (AV grafts) in the United States compared to AV fistulas and an increasing dependence on permanent indwelling silastic central catheters. Furthermore, the frequency of AV fistula placement in the US is still low compared to Europe and Canada even after adjustments for demographic differences that may influence the choice of access. The most recent report of the US Renal Data System (USRDS) indicates that 60 days after the start of HD, treatments were performed using a functioning autologous fistula in only 17.9 % of patients, while PTFE/Bovine grafts were used in 50.3%, and either a cuffed or temporary catheters in the remaining 31.8% of patients [3].

In the US, lack of early vascular access planning and type of medical care prior to onset of end-stage renal disease (ESRD) as well as socioeconomic factors result in a disproportionate number of patients initiating in-hospital HD via temporary dialysis catheters [4]. For example, in a study by Ifudo et al., temporary HD vascular access was used for the first dialysis in 100% of patients with no prior medical care and 69% of patients who received prior care from a non-nephrologist but in only 36% of patients who received prior care from a nephrologist [5].

The National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI)

recommends the increased construction of AV fistulas as the access of choice for HD as well as earlier referral of chronic renal failure (CRF) patients to nephrologists to permit access evaluation and early construction of an AV fistula or graft, thereby minimizing the use of venous catheters. Early protection of potential sites for native AV fistula construction is also of utmost importance.

After the access is constructed, the major issues relate to:

- detection of access dysfunction prior to access thrombosis;
- maintenance of vascular access patency; and
- prevention of infectious, ischemic, and aneurysmal complications.

Like many other facets of the care of the dialysis patient, improvements require that the treatment team develop and implement Continuous Quality Improvement (CQI) methodology. Dialysis centers thus need to detect vascular accesses at risk, track access complication rates and implement procedures that maximize access longevity. Achieving these goals requires the concerted efforts of nephrologists, nephrology nurses, access surgeons, vascular interventionists, patients and other members of the health care team.

Consequences of Vascular Access Dysfunction

The cost of treating ESRD patients includes not only the cost of dialysis and medications (procedural costs) but also the cost of all inpatient permanent access and outpatient temporary access-related services following access complications. Vascular access complications are reported to be the largest single cause of morbidity among HD patients and a major contributor to HD cost. The total estimated direct medical payments for the ESRD program by public and private sources in the USA was $13.06 billion in 1995. Expenses arising from access complications and their associated hospitalizations account for a substantial proportion of all expenses. The number of hospitalization for vascular access problems in 1995 was projected to exceed 90,000. At a conservative estimated cost per hospitalization of $7,500, access related costs rise above $675 million annually [6].

Estimated expenditures are likely to underestimate current total vascular access-related costs for several reasons. First, the annual cost of vascular access maintenance has been growing faster than the HD population. The total number of vascular access related hospitalization as a percentage of all cause of hospitalization has increased from approximately 17% in 1986 to > 20% in 1991 [6]. Vascular access complications can account for up to 30% of hospital admissions in some chronic HD programs [7]. About three-fourths of patients undergoing HD will be hospitalized for a vascular access-related problem during a 2-year period [8]. According to Rocco et al. a total of 2.43 inpatient days and 1.05 outpatient encounters per year are directly and solely attributable to access complications [9]. Second, the costs for hospitalization frequently quoted do not include payment by insurers other than Medicare. Third, outpatient costs for diagnostic procedures like fistulography, Doppler ultrasonography and outpatient therapeutic procedures such as thrombolysis and angioplasty are incompletely included in the estimations. Thus the annual cost of increasing vascular access related morbidity likely exceeds $1 billion/year representing nearly 10% of Medicare ESRD expenditures.

One of the most important causes for increased morbidity from vascular access is the progressive decrease in the fraction of native AV fistulas constructed relative to those of polytetrafluoroethylene (PTFE) grafts and indwelling permanent catheters. This most likely results from the interplay of several factors including a perception of higher primary failure rate of native AV fistula in older diabetic patients with peripheral vascular disease (PVD) and the relative rapid usability of PTFE grafts and permanent catheters. In the US, it is presently estimated that < 25% of ESRD patients undergo construction of the native AV fistula [6, 8, 10]. In some geographic areas, up to 85% of patients undergo HD using prosthetic grafts or permanent catheters [10]. Construction of a greater proportion of PTFE or other prosthetic graft accesses is accompanied by increased event rates that translate into increasing costs. Several studies document that the event rate in grafts is 3 – 5-fold higher than in autologous AV fistulae [2, 11, 12]. The reported complication rate for autologous AV fistulas is 5/1000 patient-months as compared to 37/1000 patient-months for PTFE grafts [11]. Mehta reported equivalent assisted patency survival for AV fistulas and prosthetic grafts for the first 2 years, but a nearly 4-fold higher procedure rate to maintain such patency in grafts [2].

Data from Wave 1 study of the USRDS reported that despite the aging of the population, native fistulas had a greater primary survival (time to first failure) than grafts [13]. Besarab et al. reported that primary and secondary patency (time to complete failure) dated from time of construction was superior in native fistulas while complication/event rates were 70% lower than in PTFE grafts [14]. Unfortunately in this study as well as in the study by Ifudu et al. [5] and Hood et al. [4], more than half of the patients requiring dialysis presented without prior adequate medical care and required urgent dialysis. Besarab et al. [14] found that the odds ratio for placement of a graft were 2.2 for females (vs. males) and 4.1 if pre-ESRD care was provided by a non-nephrologist. Age, diabetes mellitus (DM), and frequency of clinic visits had no influence on the likelihood of AV fistula placement.

Driven by cost-control issues in the 1990s, most vascular access procedures have shifted from the in-patient to the outpatient setting. This has not reversed the increased use of grafts and catheters nor slowed the increase in access-complication associated costs [3, 15, 16].

Correction of inordinate delay in access placement is simply achieved by earlier referral of patients with CRF to nephrologists. This requires a paradigm shift among MCO/HMOs with specialists assuming care for pre-ESRD patients. Initial costs are likely to increase from such early participation by nephrologists and vascular surgeons. However, such early participation can significantly reduce the need for temporary catheters, reducing not only the direct procedural costs but also indirect hospitalization costs associated with catheter complications (pneumothorax, hemothorax, and sepsis). A mechanism for providing health care to the uninsured pre-ESRD patients must also be developed.

The other major source of costs attributable to vascular access arises from non-mechanical complications. Chief among these is access-related infection and bacteremia. Within our system of > 800 HD patients, almost half of the vascular-access related admissions result from line-related sepsis (temporary or permanent catheters). Infectious complications are a source of substantial morbidity and a common cause of death among HD patients, accounting for about 20 – 25% of all vascular access complications [12, 17, 18]. Data from

1995 USRDS indicate that 12% of all deaths among HD patients is attributable to infection [19]. Septicemia is the underlying cause in 76% of these infectious deaths. Sepsis from vascular access accounts for 12 – 25% of these septicemia-related deaths [19, 20]. Among HD patients, Keane et al. reported an average of 7.6 bacteremic episodes/100 patient-years, 48% of which were associated with access infections. AV fistulas have a much lower rate of infection than PTFE grafts [21, 22] or catheters [23].

Despite the considerable economic resources committed to the care of ESRD patients in the USA, death rates adjusted for age, race, gender and primary diagnosis during the first year of dialysis therapy remain high [24]. Cox proportional hazards models, stratified for DM, have examined the effect of delivered dose of dialysis on major causes of death after adjustment for other demographic covariates and comorbid diseases. These results indicate that low dose of dialysis is associated with a number of the major causes of death in the ESRD population [25]. Low doses of dialysis may promote atherogenesis, infection, malnutrition and failure to thrive through a variety of pathophysiologic mechanisms. HD vascular access dysfunction is an important cause for inadequate dose of dialysis.

Close attention to vascular access management has great potential for improving quality of life and overall outcomes for HD patients. The high overall costs and the large fraction of costs that still accrue from inpatient settings clearly indicate that opportunity for savings exist from optimizing vascular access care. The quality of life for dialysis patients in any center may reflect the standard of its vascular access service with poor access causing significant morbidity and mortality.

HD Vascular Access Types

The need for vascular access in patients with renal failure can be either temporary or permanent. Need for temporary access may vary from several hours (single dialysis) to months (if used to bridge maturation of a primary autologous AV fistula). Temporary access is usually established by the percutaneous insertion of a catheter into a large vein (preferably femoral or internal jugular; subclavian is less desirable).

Venous Catheters

As Acute Access for HD: These provide rapid and temporary access for HD. Uncuffed dual lumen central venous catheters are preferred because of the ease of insertion and immediate usability. They are inserted only when required and when functioning well these catheters provide blood flow rates of 250 – 300 mL/minute with a recirculation of < 2%. If the ports of the catheters are reversed the recirculation rate can increase up to 20%, compromising the adequacy of dialysis especially in hypercatabolic patients [26]. The common situations requiring acute vascular access are summarized in Table 1.

As Permanent Access for HD: Soft silastic cuffed catheters are emerging as an alternative form of long-term vascular access for patients in whom a permanent AV access cannot be readily created. Table 2 lists the indications for use of these catheters as permanent access.

These silastic catheters can be used for extended period of time and presently account for 10 – 15% of the permanent vascular access in most dialysis centers [27]. However, survival rates for cuffed double-lumen catheters are about 60% at 6 months and 40% at one

Table 1. Indications for Acute Vascular Access

1. Acute renal failure requiring HD
2. Chronic renal failure patients needing urgent HD but without available mature access
3. Maintenance HD patients who have lost effective use of their permanent access and require temporary access until permanent access function can be re-established
4. Peritoneal dialysis patients whose abdomens are being "rested" prior to new peritoneal catheter placement
5. Transplant recipients needing temporary HD during severe rejection episodes
6. Patients requiring plasmapheresis or hemoperfusion

Table 2. Indications for Catheters as Permanent Vascular Access

1. Small children
2. Diabetic patients with severe vascular disease.
3. Morbidly obese patients
4. Patients with multiple failed AV access insertions in whom additional insertion sites for AV access are not available.
5. Patients with cardiomyopathy unable to sustain adequate blood pressures or access flows.
6. Patients who require frequent blood access (daily nocturnal home HD)

year if revisions are included [28]. A primary dysfunction rate of 2% and an infection rate of > 50%/year has been reported [29]. Adequate blood flow through cuffed venous catheters is a significant problem. Although such silastic catheters have a nominal blood flow rate of 400 mL/min in 73% of cases [28], actual flow rates of 350 mL/min can rarely be sustained and usually flow is limited to a value closer to 300 mL/min. These low flows have limited the use of permanent cuffed venous catheters in larger patients receiving high flux dialysis since adequate dose of dialysis (*Kt/V*) is difficult to achieve in < 4 hours. The advantages and disadvantages of tunneled cuffed catheter relative to other permanent access are shown in Table 3.

Because of the limitation of blood flow of most double lumen catheters, recent interest has focused on use of twin silicone rubber catheters (Tesio catheters), each with its own cuff for either long-term temporary or permanent access [30]. A higher flow rate with these catheters is claimed. Although mean flow rates (blood pump setting) are in the range of 400 mL/min, actual measured blood flow is 360 mL/min [31]. Other advantages of the Tesio catheters (none proven in randomized trials) are increased patient comfort, less positional dysfunction (as the outlet ports are wound spirally around the distal parts of each catheter), and perhaps increased longevity. However, they are more difficult, to place initially than other catheters.

Catheter material: Thrombogenicity and flexibility primarily determine the choice of the material. Acute catheters are typically made of polymers such as polyurethane, polyethylene and PTFE. Polyurethane is chemically stable and appears to offer the best balance between rigidity at room temperature and flexibility at body temperature and has less thrombogenic potential compared to other materials [32]. Soft silastic (silicone elastomer) catheters are the most pliable and least thrombogenic and produce less trauma to the vascular intima. Initial designs required peel-away sheaths for their percutaneous insertion. Newer designs have overcome this by incorporating an internal stylette. Incorporation of antimicrobial substances in the catheter material may reduce the rate of catheter-related infections.

Table 3. Advantages and Disadvantages of Tunneled Catheters as Permanent Access

Advantages	*Disadvantages*
– Universally applicable	– High morbidity from infection and thrombosis
– Multiple insertion sites	– Risk of central vein stenosis and occlusion
– No maturation time	– Discomfort and cosmetic effect of external appliance
– No hemodynamic consequences	– Shorter useful life span
– Ease and cost of placement	– Lower blood flows
– Ease of correcting thrombotic complications	
– No venipuncture requires	

Catheter Design: Dual-lumen venous catheters have one of 2 basic cross-sectional configurations for the 2 blood pathways: either a "double-D" configuration or a coaxial cylinder configuration. The double-D design delivers a higher blood flow rate [33]. The arterial ports are placed typically 2 – 3 cm proximal to the venous port to minimize recirculation. Advancement in catheter design, especially development of curved shafts in acute catheters, increases patients' acceptance because such catheters can be easily secured, allowing free head and neck movements.

Use of an uncuffed catheter for periods of time beyond several weeks results in a relatively high rate of infection. Bonded felt or Dacron cuffs were added to extend the use of venous catheters from weeks to several months by reducing line-related infection and catheter migration. Unequivocal demonstration that cuffs prevent infection has not been shown [34]. Cuffed catheters require "surgical" tunneling for placement, further increasing the complexity of the procedure. Therefore, non-cuffed catheters are usually chosen when the need for HD is projected to be < 3 weeks in duration, although some centers use cuffed catheters routinely for cases of acute renal failure (ARF), when the duration is expected to extend beyond 1 week. Cuffed silastic catheters are preferred if the need for dialysis is > 3 weeks duration. Use of cuffed catheters is especially useful when one is planning to or has just placed an AV fistula, which requires several months to mature properly.

Insertion sites: Uncuffed double-lumen catheters are inserted percutaneously by the Seldinger wire technique. The preferred site for both uncuffed and tunneled cuffed catheters is the right internal jugular vein, which offers a more direct route to the caval-atrial junction and together with its softness and flexibility causes less intimal trauma. The subclavian site should generally be avoided because of the high incidence of venous stenosis and thrombosis associated with its use that can compromise the creation of AV fistula or graft in the ipsilateral arm [35]. The rate of other complications (e.g. pneumothorax) related to subclavian vein cannulation is also higher compared to jugular vein insertion [36]. According to the NKF-DOQI recommendations, subclavian access should be used for cuffed catheters only when jugular options are not available and the tunneled cuffed catheter should not be placed on the same side as a maturing AV access.

Use of a portable real-time ultrasound to guide insertion is recommended to reduce

insertion-related complications. The central veins of the neck exhibit significant anatomic variability and one of them may occasionally be absent [37]. Atypical or ectatic carotid arteries are also a problem. The rate of successful internal jugular puncture on the first attempt increases 2-fold to > 80%, and the rate of carotid artery punctures is reduced from 8 to 0% when insertion is performed under ultrasound guidance [38]. The principal disadvantage of the jugular vein approach is that the catheter is difficult to fix to the skin in this position and neck mobility is impaired. These disadvantages can be overcome by tunneling over the clavicle to the skin exit site on to the anterior chest wall. The optimal tunnel design has not been clearly established. For the catheter inserted into the superior vena cava, curved tunnels permit smooth passage of the catheter to the anterior chest wall. Similarly curved tunnels permit approach from the lateral abdominal wall to the inferior vena cava. They therefore provide comfort to the patient and minimize kinking. Cuffed catheters are commonly used but are not necessary as long as the catheter is secured to prevent migration.

Fluroscopy is mandatory for insertion of all cuffed upper extremity dialysis catheters since the catheter tip has to be adjusted to the level of caval-atrial junction or beyond to ensure optimal blood flow and to ensure that complications have not occurred. Femoral catheterization is the preferred choice for most emergencies like pulmonary edema (the patient's head and chest can be kept elevated during insertion) or acute poisoning (catheter requirement is usually only several days) but the catheters should be ≥ 19 cm long to minimize recirculation. The increased rate of infection up to 10% at one week, along with the high dislodgment rate mandates the uncuffed femoral catheters to be left in place for no more than 5 days.

Arteriovenous (Scribner-Quinton) Shunt

The surgical implantation of paired, interconnected plastic tubes into an extremity artery and a nearby vein, first introduced in 1960, is now mostly of historic significance. The long-term usefulness of this vascular access method is limited by the need to sacrifice vessels. Patency of the shunt depended on the continuous flow of blood through it and provided extra-corporeal flows of only 200 mL/min, a flow too low for most modern HD. The Scribner-Quinton shunt is plagued by a multitude of problems chief among these being a high rate of thrombosis, recurrent infection, and the risk of accidental dislodgment. This form of access should never be used if there is even a slight possibility that the patient's condition will eventually require chronic HD. Double-lumen catheters have largely replaced it.

Complications of Catheters used for Acute Access

Insertion-related complications: Placement of dual-lumen catheters for temporary or permanent HD is associated with many short and long term complications. Although specific complications vary with site of insertion, distortion of the anatomical landmark from obesity, trauma, surgery, radiation, previous hematoma or other unrecognized vascular anomalies and the presence of coagulation disorders increases the rate of complications. The complications associated with insertion of catheters for HD is summarized in Table 4. Acute complications are defined as those occurring immediately or within several hours. Delayed complications may not occur for days or weeks.

Table 4. Complications of Catheter Access Insertion into the Superior Vena Cava

Acute complications	*Delayed complications*
External bleeding	Venous thrombosis
Subcutaneous hematoma	Venous stenosis
Internal bleeding	Sternal osteomyelitis
Hemothorax	Bacterial endocarditis
Pneumothorax	Artery to vein fistula
Air embolism	Hydromediastinum
Hemothorax/hemomediastinum	Superior vena caval syndrome
Cardiac tamponade	Pulmonary embolism
Damage to blood vessel	Unilateral breast enlargement
Arterial perforation	Chronic massive arm edema
Perforation of SVC	
Perforation of the thoracic duct	
Perforation of the trachea	
Perforation of the myocardium	
Damage to the brachial plexus, peripheral nerves or cervical sympathetic chain	
Acute bacteremia/septicemia	

The overall success of superior central vein cannulation and the complication rate depends upon the physician's experience and the use of ultrasound to localize the vein [36 – 40]. The sum of all major immediate complications should not exceed 5% of all central venous catheter placements. Subclavian vein cannulation carries a greater risk for immediate and late complications compared to the internal jugular approach [41]. Arterial puncture is a common complication of central line insertion. Direct compression is not possible in subclavian arterial puncture, resulting in serious hemorrhagic complications in 1% of the patients.

Prior to the use of ultrasound guidance, pneumothorax complicated 1 – 5% of the subclavian catheterization compared to < 1% with internal jugular cannulations [36, 39]. However, a 7 – 16% failure rate in accessing the internal jugular vein has been reported even when performed by experienced operators, probably as a result of aberrant anatomical position of the internal jugular vein in 14% of cases [42]. Puncture-related complications occurred in up to 11% of the cases [43]. Ultrasonographic-guided internal jugular vein cannulation increases the success rate of first attempt cannulation from < 40 – 60% to > 85% along with lower rates of complications [38, 44].

Myocardial irritation from guide wire or catheter contact produces atrial arrhythmias in up to 40% and ventricular arrhythmias in 10% of patients, but fortunately < 1% require anti-arrhythmic medication [45]. More serious life-threatening complications of central vein cannulation include perforation of vessel wall or atria leading to hemothorax or cardiac tamponade, respectively. Rare complications include strokes from paradoxical cerebral embolism from the catheter tip or atrial thrombus via a patent foramen ovale. Bleeding caused by heparin block or accidental disconnection

of the catheter clamp and cap can lead to exsanguination.

During femoral vein cannulation, inability to cannulate the vein results mostly from distortion of the anatomy since vascular anomalies in the femoral triangle are extremely rare. The common complications are arterial puncture and hematoma. Rarer complications include iliofemoral thrombosis, pulmonary embolism and retroperitoneal hematoma. As with internal jugular vein catherization, ultrasound guidance as compared to external land mark technique increases the success rate of femoral vein cannulation from 89.5% to 100% and reduces the complication of arterial puncture from 15.8% to 7.1% and that of hematoma from 2.6% to 0% [40].

HD access infection: Infection is the leading cause of catheter loss and as discussed previously increases morbidity and mortality [16 – 20]. Roughly one-fourth of all vascular access-related hospitalizations are attributed to access-related infection or inflammatory disorder [8]. In the most recent USRDS (1997) report, the fraction of adult HD patients dying of infection was 15.5%; access infection contributes significantly to this percentage. Even for dual-lumen tunneled cuffed catheters, the infection rate is 3.9 to 9 episodes/1000 catheter-days at risk, a value not different from that of 1.6 to 8.6 episodes/1000 catheter-days for uncuffed, untunneled catheters [34]. The mortality directly attributed to the use of central venous catheters appears to be in the range of 1% [35].

Pathogenesis: Infection usually arises from the migration of the patient's own skin flora through the puncture site and onto the outer catheter surface, although it can also result from contamination of the catheter connectors or lumen contamination during dialysis. Catheters can also become colonized from more remote sites during bacteremia. Colonization of the intravascular portion of the catheter will generally express itself as a febrile episode during HD. Gram-positive bacteria (usually *Staphylococcus* species) are the most frequent organisms.

Classification: Infection of cuffed HD catheters is traditionally subdivided into exit site infection, tunnel infection and catheter-related sepsis. An alternative classification is provided in Table 5.

Risk factors and Prevalence: Factors contributing to catheter infection are listed in Table 6. The most important factor producing infection is the duration of catheter use. Immunocompromised patients, drug addicts, and patients with a previous episode of bacteremia are at increased risk for catheter-related bacteremia. The incidence of infection of central vein uncuffed catheters is generally < 8% by 2 weeks. By one month, 25% of uncuffed central catheters become infected and this figure doubles by the end of the second month. Catheter-related septicemia may occur in 2 – 20% of catheters. An infection of the exit site or subcutaneous tunnel infection has not been prominently reported as a precursor of catheter-related bacteremia

Table 5. Diagnosis of Central Venous Catheter Infection

Definite infection
– Erythema and tenderness along the catheter tunnel
– Fluctuance along the tunnel
– Loss of adhesion of anchoring cuff
– Purulence at exit site
Probable infection
– Sepsis without definite alternate source
– Fever >38 °C
– Rigors especially during dialysis
Possible infection
– Low grade fever
– Leukocytosis

Table 6. Factors Contributing to Catheter Infection

– Duration of the catheter use
– Immunocompromised status
– Nutritional status and co-morbidity factors such as diabetes
– Nasal *S. aureus* carriage
– Type of dialysis membrane
– Type of HD procedures and insertion techniques
– Injection drug use and previous bacteremic episodes

in HD patients. Infectious complications particularly septicemia ultimately limit the longevity of the indwelling catheters in at least 25% of patients.

Bacteriology: Gram-positive cocci, particularly *S. aureus,* account for 53 – 63% of all catheter-related bacteremias; 24% are due to gram-negative rods, and 11 – 12% due to multiple organism [34, 46]. Metastatic complications such as endocarditis, bone and joint infections have been reported in up to 23% of catheter-related bacteremia and up to 41% with *S. aureus* infection [34].

Management: There is no universal agreement about the management of cuffed HD catheter infection. Ideally all infected catheters should be removed, a stance limited by the practical necessity of maintaining HD access site in patients who have lost all other access sites. Localized exit site infections can be treated with systemic antibiotics combined with local care often without loss of the catheter. Patients with tunnel infection, abscesses or loss of anchoring of the cuff should have the catheter removed, as there is no hope of salvage. Salvage of the catheter in patients with catheter-related bacteremia without tunnel infection and catheter salvage is successful in only 32% of cases [34].

Attempting salvage of central venous catheters in patients with limited or no other access sites should be done carefully with frequent monitoring of the patient for signs of sepsis and blood cultures for continuing bacteremia during therapy. Initial antibiotics should cover both gram-positive and gram-negative organisms. Once cultures are available, the antibiotics can be tailored and therapy continued for up to 4 weeks. In difficult cases, antibiotics can be *"locked"* in the catheter between dialysis sessions in addition to the use of systemic antibiotics. The patient must be observed closely for signs and symptoms of sepsis particularly during HD. If these or hemodynamic instability, evidence of a tunnel infection, positive surveillance cultures during therapy, or metastatic infection develop, the catheter must be removed. If a new site is not available, an attempt at salvage can be attempted by changing the catheter over a guidewire [47]. Prolonged attempts to salvage an infected, cuffed catheter can lead to serious complications (endocarditis, osteomyelitis, suppurative thrombophlebitis). Spinal epidural abscess is a rare but serious neurological complication in HD patients. In one series, 50% of cases were associated with attempted salvage of an infected cuffed venous catheter [48].

Prevention of catheter infection is of prime importance. The use of dry gauze dressing and povidone iodine ointment at the catheter exit site can reduce the incidence of exit site infections. Surgical masks worn by the patient and nurse at any time the catheter is accessed reduces the spread of nasal droplet infection. Catheter hubcaps or blood line connectors should be soaked for 3 – 5 min in povidone iodine and than allowed to dry prior to separation and the catheter lumen should be kept sterile at all times and never remain open to the air. Prophylactic antibiotics should be given for procedures likely to produce bac-

Table 7. Types and Management of Catheter Thrombosis

Types of catheter thrombus	*Management*
Intracatheter (or) Luminal	Avoid forced irrigation, Intraluminal thrombolytics
Extracatheter	
Fibrin sleeve	Catheter venogram, low dose thrombolytics for 24 hours, catheter stripping.
Mural thrombus	Catheter removal, anticoagulation, catheter-directed thrombolysis. Surgical thrombectomy as last resort.
Ball valve thrombus	Catheter removal, anticoagulation therapy.

teremia (dental work, sigmoidoscopy, colonoscopy, and endoscopic retrograde chloledochopancreatography (ERCP)).

Catheter Dysfunction: This is a most vexing problem. It is classified as intracatheter, fibrin sleeve, or mural and the specific site of catheter obstruction may require diagnostic studies: catheter venograms, venograms, or intravascular ultrasound. When it occurs early, it is due either to malposition or to intracatheter thrombosis. Many dysfunctional catheters exhibit positional occlusion during dialysis. Early catheter dysfunction (< 5 days from insertion) is usually the result of intracatheter thrombosis or catheter malposition. Late dysfunction results from fibrin sleeves or mural thrombosis. The classification and management of catheter thrombosis is summarized in Table 7.

Intracatheter thrombosis (luminal obstruction) is the most common complication occurring in up to 10% of all dialysis treatments with cuffed silicone catheters [49]. These are easily detected since they interfere with extracorporeal blood flow. Most of these will respond to intraluminal thrombolytic injection of urokinase. It is important to initially fill the dead space of the catheter lumen with the thrombolytic agent and inject 0.3 ml of heparinized saline at 5 – 10 min intervals in order to permit the thrombolytic to reach and work on the clot. More than one instillation of urokinase may be necessary to re-establish patency. Patency is restored in 90 – 95% of cases.

Malposition or catheter tip thrombus presents as persistent low flow despite urokinase treatment. Fluoroscopy with or without contrast injection is needed for diagnosis. Large catheter tip thrombi usually require systemic thrombolysis (urokinase 20,000 U/hour for 6 hours or streptokinase 3000 U/hour for up to 24 hours). If a thrombus is absent and access sites are limited, the catheter can be changed over a guide-wire, but the problem is likely to recur.

Fibrin sleeves are the most common reason for late dysfunction. Virtually all central vein catheters develop a fibrin sleeve within one to several weeks after insertion. Fibrin sleeves are initially clinically silent until they obstruct the ports at the distal end of the catheter.

Saline infuses into a port easily but aspiration is difficult due to a check-valve effect. Fibrin sleeves can serve as a nidus for infection as well. A catheter venogram should be performed to confirm the diagnosis. A variety of methods can be used to handle fibrin sheaths. Low-dose systemic thrombolytics (urokinase 20,000 U/hour for 6 hours or streptokinase 3000 U/hour for up to 24 hours) are usually the first option. If unsuccessful, advancement of a snare from the femoral vein up the inferior vena cava to the occluded catheter permits stripping of the fibrin sheath. The adherent fibrin sleeve/thrombus pulled from the catheter usually embolizes into the lung. Clinically evident pulmonary embolism has been reported from this procedure, but is unusual. Alternatively because of the expense of snare catheter stripping, some centers merely exchange the catheter over a guidewire since it has been shown to be as effective as snare catheter stripping in the case of fibrin sleeve formation.

Mural thrombi usually develop at the vessel wall and can result in permanent vessel occlusion. Large mural thrombi can proceed to stenosis and central vein thrombosis. The usual manifestations consist of limb edema and distended or varicose collateral veins secondary to venous obstruction. A clot adherent to the end of the catheter is a *ball thrombus. Right atrial thrombus* result from an injury to the endocardium. Pulmonary embolism from mural thrombi or catheter-related thrombi is fortunately rare but can occur weeks or months after catheter removal, presumably by ongoing growth of thrombus on an injured endothelial surface. Diagnosis is best made by venography through the catheter. This problem is best handled by catheter removal followed by systemic anticoagulation, and if it is still refractory, radiologically-directed thrombolytics. Surgical thrombectomy is the method of last resort.

The incidence of early dysfunction due to malposition is strongly dependent on the experience of the person performing the insertion. Tesio type silicone catheters may have a lower incidence of positional dysfunction due to the spiral winding of their exit holes around the distal 3.5 cm of each catheter. Silicone catheters appear to have less fibrin formation than other catheter materials. Although chronic administration of warfarin or other anticoagulants may limit fibrin sleeve formation and catheter thrombus formation, there is no systematic study examining use of anticoagulants for this purpose. If used, we believe that systemic anticoagulation is required with International Normalized Ratio (INR) of 2 to 2.5 (personal experience).

Central Vein Stenosis: This is one of the more severe complications arising from the use of catheter access. Endothelial injury occurs at the site of catheter-endothelial contact. The major risk factors for central venous stenosis are use of stiff non-silicone catheters, associated catheter infections and prolonged use of catheters. Subclavian vein thrombosis or stenosis has been reported to follow 20 – 50% of subclavian catheter insertions. Surveillance venograms 6 months following catheter removal show a 3-fold higher rate of subclavian vein stenosis among patients with previous catheter-related infections than in those free of such infections [50]. The incidence is lower in the internal jugular vein as compared to subclavian vein approach (10% vs. 42%) [51]. Once a stenosis develops it may be asymptomatic and remain clinically silent until unmasked by the creation of AV fistula. Symptoms invariably are those of gross edema of the entire arm and in extreme cases venous skin ulcers. When the stenosis develops after an access has been placed, development of the edema is slower. Initial management with anticoagulation and elevation of the arm may ameliorate the symptoms and signs.

Angioplasty can definitely restore the patency but restenosis is common. Stent placement following angioplasty is indicated in elastic central vein lesions or if the stenosis recurs within a 3-month period. Ligation of the vascular access produces the most rapid improvement, but sacrifices the access. Some patients may be candidates for surgical axillary-internal jugular bypass of the affected subclavian vein. Pulmonary embolization is rare.

In summary, central venous catheters provide acceptable acute access for HD, but their use is fraught with a number of problems. Chief among these is the development of central vein stenosis that frequently precludes the establishment of a more permanent access. Infection remains a major problem. Impregnation of catheters with antiseptic substances may reduce the incidence of infection. To date, no catheter material or placement technique has the requisite properties that minimize trauma to the endothelium. Catheterization of the subclavian vein should be minimized in anyone potentially at risk for ESRD who might require future permanent access.

Permanent Arteriovenous (AV) Access

Since vascular access failure is the major cause of morbidity and hospitalization for HD patients, the NKF-DOQI has enumerated 4 key issues relating to vascular access care in HD patients. At the heart of the recommendations is the need to create a higher proportion of native AV fistulas that provide long-term access with the fewest access procedures [4, 10, 14]. Anticipation of need is paramount.

Protection of the cephalic veins, especially of the nondominant arm, is crucial in patients with progressive renal failure. This permits construction of native AV fistula preferably at the wrist and, if not possible at this site, then at the elbow.

The need for AV fistulas should be anticipated in advance of the need to initiate HD. This requires earlier referral of CRF patients to the nephrologist for planning of dialysis modalities and advanced discussions about access construction. If a native AV fistula is not possible, access may be established using a PTFE graft or a transposed brachial-basilic vein fistula. If all of the above measures are still not possible, then placement of a cuffed tunnel central venous catheter as a permanent vascular access is appropriate.

Periodic monitoring of the accesses for hemodynamically-significant stenosis prior to thrombosis is necessary. If present, expeditious management by angioplasty or surgical revisions is necessary. This minimizes the number of catheters needed and reduces the risks of underdialysis from catheters.

Educational programs on the importance of the care of the vascular access should be provided to patients and to care providers.

Preoperative Evaluation

Characteristics of the patient's arterial, venous, and cardiopulmonary systems determine the access most suitable for a given patient. Life expectancy may also influence the type and access location. Comorbid conditions like severe coronary artery disease or malignancy that limit life expectancy may preclude anything but a cuffed catheter as permanent access. Patients who are likely to undergo preemptive living transplantation might also not require permanent vascular access surgery.

History: Crucial features in the history are previous placement of a central venous catheter or transvenous pacemaker because of the possibility of vein stenosis. Hemodynamics

and cardiac function in a patient with marginal heart function can be adversely affected by any AV access. History of arterial or venous vascular disease or the presence of DM also limit access construction options. Previous surgery or trauma to the arm, chest, or neck can limit access site construction.

Physical Examination: Examination of the arterial and venous systems supplemented by hand-held Doppler when necessary is usually sufficient. The blood pressure should be measured in both arms, an Allen test performed, and arm sizes measured and compared. The patient should be examined for evidence of previous central vein catheterization and for trauma or surgery of the arm, chest or neck. Some surgeons perform tourniquet-assisted venous mapping to select the best veins for access. In patients with progressive renal disease, every attempt must be made to preserve upper extremity veins that can be used to construct future accesses. The presence of 6 cm segment of cephalic vein at the wrist is needed to create a wrist AV fistula. Whenever possible, construction of AV fistula is preferred but not always possible.

Radiologic Studies: Doppler ultrasound or venography may be required to exclude central vein stenosis [52]. Indications include edema in the extremity, collateral veins around the shoulder or on chest wall, differential extremity size, previous or current transvenous pacemaker, and multiple previous access constructions in the extremity. Doppler measurement of brachial artery flow > 80 mL/min prior to access construction is predictive of maturation of access [53]. Doppler venous studies may also identify suitable veins for AV construction that are not readily visible on the surface. Arteriography is done only if pulses in the desired access location are markedly diminished or absent.

Anticipating the need for autologous access fistula construction: This requires that venipuncture or placement of intravenous (IV) catheters into forearm veins be minimized in patients with progressive renal failure. The dorsum of the hand should be used. The AV fistula should be created 4 – 6 months prior to the initiation of HD; the latter can be anticipated from the rate of rise of the plasma creatinine level. Patients should be referred to the surgeon when the serum creatinine is > 4 mg/dL.

Construction in patients on peritoneal dialysis (PD): With the increased ability to bridge PD patients through a period of temporary loss of peritoneal access (from catheter obstruction, infection, leakage, or hernia) by using percutaneous venous catheters, the previous common practice of creating an AV fistula in patients planning to start PD has been abandoned by many centers. However, the high incidence of catheter malfunction, peritonitis, and technique failure places these patients at risk each time a temporary catheter has to be placed, a risk avoided by AV fistula creation [54].

Construction principles: The surgical consensus as articulated by Palder et al. [55] promotes the use of the non-dominant arm, beginning as distally as possible and moving up the arm proximally as access fails. When all sites in the non-dominant arm have been exhausted, the dominant arm is used.

Autologous Arteriovenous Fistula

These fistulas consists of a subcutaneous anastomosis of a artery and an adjacent vein. Maturation, a process of dilatation and thickening of the wall of the venous limb of the fistula to permit repeated insertion of dialysis needles requires 3 – 4 months. Therefore, an AV fistula should be constructed in advance of the need for HD. The fistula is usually created in the non-dominant arm to facilitate

self-dialysis and limit the consequences of any functional disability should any occur.

Characteristics: AV fistulas are the safest and the most durable permanent vascular accesses. Their advantages compared to other access types include excellent patency, lower morbidity associated with their creation, and lower complication rates (infection, stenosis, and steal). For equivalent degrees of assisted patency, the AV fistula requires a 3 – 4-fold lower number of procedures [4, 14]. Disadvantages include the long maturation time as well as failure to develop adequate blood flow sufficient to support the dialysis prescription in some patients.

Creation of an adequate AV fistula may not be possible in some diabetic patients or those with severe atherosclerotic arterial disease. Marked obesity, the presence of small or deep veins, or veins damaged by multiple venipunctures may also limit the possible creation of an adequate AV fistula. It is generally believed that elderly patients are less likely to have suitable anatomy to create an AV fistula. In our experience, age has not been a factor, although more attention must be paid to maturing the access [14]. Doppler ultrasound mapping studies may identify veins not readily apparent to nephrologist or surgeon.

Construction: Wrist radial-cephalic *(Brescia Cimino 1966)* and elbow brachial-cephalic AV fistulas are the 2 types most often created. Other options include a "snuff-box" fistula, wrist ulnar-basilic and a transposed elbow brachial-basilic fistula. The anastomosis can be made either side-of-artery to side-of-vein or side-of-artery to end-of-vein. In both instances, blood flow through the artery distally is preserved. With the side-to-side method, higher pressure may sometimes be transmitted to the veins in the hand resulting in venous hypertension and swelling. The side-of-artery to end-of-vein anastomosis prevents venous hypertension of the hand because the distal vein is tied. The surgery is usually performed in the operating room under regional anesthesia. Details of the operative technique are beyond the scope of this chapter.

Postoperative care: The arm should initially be kept elevated. Tight circumferential dressings must be avoided. The fistula blood flow should be checked several times during the first 24 hours and then daily by palpating for a thrill at the fistula site and by listening for the associated bruit. The fistula should never be used for venipuncture. Failure to develop superficial veins of the fistula may result from inadequate arterial (brachial or radial artery) inflow, from an anastomotic stenosis due to fibrosis or from flow into deep side branch veins. In the latter situation (diagnosed by venography), ligation of such veins may result in successful maturation.

Maturation: This is a process of dilatation and thickening of the wall of the venous limb of the fistula and is necessary in order to repeatedly insert dialysis needles. Maturation of the AV fistula takes from 1 – 6 months. Regular hand exercises with or without a lightly applied tourniquet can aid in access maturation. An AV fistula should not be used before it is mature. Use of percutaneously placed cuffed catheters can bridge the period of several months if dialysis is needed prior to AV fistula maturation. Premature access cannulation is associated with infiltration and compression of the vessel and with permanent loss of the fistula. Infiltrated fistulas should be rested.

Arteriovenous Graft

When an adequate autologous AV fistula cannot be created, the AV connection can be made using *a tube* graft made from a variety of synthetic or biologic materials. Synthetic

polytetrafluoroethylene (PTFE) grafts are the preferred materials since they provide superior performance compared to biologic bovine heterografts. Dialysis AV grafts can be tapered or uniform, externally supported, thick- or thin-walled. AV grafts have the following advantages over AV fistulas:

– easy surgical handling characteristics,
– easy cannulation,
– large surface area, and
– short maturation time.

Long term patency of an AV graft is inferior to an AV fistula despite a 3 – 4-fold increase in salvage procedures.

Configuration and location: Grafts may be placed in straight, looped or curved configurations. The location is determined by patient-specific features as well as the projected length of the need for HD. In general, more distal placement preserves potential sites but such grafts may experience more frequent bouts of thrombosis. A distal graft (e.g. straight forearm graft from radial artery to an antecubital fossa vein) can sometimes be used to mature an upstream vein for future AV fistula construction. The most common initial sites for AV graft placement are in the non-dominant forearm and include a straight graft from the radial artery at the wrist to the basilic vein, a loop graft in the forearm from the brachial artery to the basilic, or an antecubital vein or an upper arm graft from brachial artery to axillary vein. The anastomoses in all instances are made between the end of the graft and the side of the vein or artery, minimizing interference with blood flow through the native vessels. The axillary artery can be used for loop grafts in the upper extremity. The graft can extend from the arm to the internal jugular vein to bypass a subclavian stenosis on the same side.

Grafts can also be placed in the thigh, although such placement is associated with a higher complication rate. Thigh grafts are usually attempted after upper extremity sites have been exhausted. Long-term dialysis patients frequently have had both upper extremities used for access. In extreme cases, chest wall grafts (necklace) have been constructed. All grafts should maximize the surface area for cannulation.

Surgical placement: AV grafts are placed in the operating room under regional anesthesia (with backup for general anesthesia) by a surgeon skilled in performing vascular anastomoses. Prophylactic antibiotics (e.g. second-generation cephalosporins) are commonly administered immediately prior to the operation. Short length grafts have no advantage over long grafts in terms of patency and longevity and should not be constructed. Whenever possible the graft should maximize surfaces available for cannulation and permit good site rotation. Postoperative care of grafts is the same as that for fistulas. The extremity is kept elevated for several days and graft function is checked regularly by assessing for venous pulsation, thrill, and bruit. Most constructions are now performed on an outpatient basis. Because of anatomical variations in veins, the surgeon should provide a “road map” of the access for future reference. This is particularly important if a loop is reversed and the arterial limb of a loop graft is not on the medial side of the forearm.

Maturation of AV grafts: Although some surgeons and nephrologist have advocated use of a AV graft for dialysis within 1 – 2 days of its construction, adhesion of the subcutaneous tunnel and graft requires about 2 weeks. Hematoma in the tunnel from early cannulation can compress and ruin the access. In most circumstances, the use of AV grafts should be delayed for 2 – 3 weeks if possible to allow for healing of the subcutaneous tunnel and incorporation of the graft into the tissues. Temporary catheters can be used if urgent

dialysis is needed. A graft is considered mature when edema and erythema have resolved and the graft course is easily palpable. Cannulation of a graft that cannot be easily palpated or is edematous invites inaccurate needle insertions, leading to hematoma formation or frank laceration. In some patients, erythema along the course of the graft develops within the first several days. This is a normal variation of the healing response and not necessarily indicative of graft infection or cellulitis.

PTFE grafts reinforced with additional layers of fiber windings have been marketed and promoted as having the desirable property of undergoing cannulation within 5 days of insertion. The additional extra windings ostensibly limit the extravasation of blood on needle withdrawal and the accompanying risk of perigraft hematoma formation. Grafts withstanding early cannulation would reduce or eliminate the need for a venous catheter access as a bridge for the maturation. Despite initial enthusiasm, however, the first of such early use grafts has not been widely adopted. They are more difficult to insert without benefits of patency. In fact, they appear to have a lower patency rate and possibly a higher rate of infection.

Access Cannulation

Needle size: During the initial use of a permanent vascular access, some nephrologists recommend the use of smaller 16-gauge needles and lower blood flow rates of 200 – 250 mL/min, particularly in AV fistulas. In mature accesses, larger 15-gauge needles are needed to support the higher blood flow rates of 350 mL/min or greater needed for high-efficiency or high-flux dialysis.

Needle orientation and placements: Two needles are placed into the dilated vein(s) of the AV fistula or graft. In an autologous fistula, the arterial needle leading to the dialyzer blood inlet is always placed in the more distal segment of an access but at least 3 cm away from the AV anastomotic site. The arterial needle may point either toward the heart or the hand. The venous needle should be inserted pointing toward the heart ≥ 5 cm proximal to the arterial needle. In a graft the venous needle should be inserted into that part that is closest to the venous anastamosis. Separation of the needles is needed to minimize recirculation. Pointing the arterial needle toward the heart is popular in many countries, since the "flap" left behind following needle withdrawal tends to close more naturally with the flow of blood. There is, however absolutely no evidence that this in fact aids in hemostasis or reduces insertion-related complications. Some caregivers advocate 180° rotation of each needle after insertion. Whether this actually reduces injury to the back wall of the access has not been systematically studied.

Special care must be taken during cannulation of forearm loop grafts. In > 80% of such grafts, the arterial limb will be medial (ulnar), but in the remainder the arterial limb may lie on the radial side of the forearm. A "road map" of the access from the surgeon is very useful but not always available as patients may be operated on at another center, and a diagram or description of the inserted access may not be readily available. Inadvertent reversal of needle placement substantially increases the amount of recirculation to a mean of 20 – 25%, an amount that produces inadequate delivery of dialysis. When in doubt, a careful physical examination with transient occlusion of the access and palpation on either side of the occluding finger will reveal the direction of blood flow in almost all cases. The arterial limb is the side with a pulse. Transient occlusion does not injure the access.

Needle placement strategies: The manner in which needles are inserted affects the long-term patency and survival of accesses, particularly AV fistulas. The "ladder" or rotational approach uses the entire length of the access without localizing needle sticks to any 2 areas. Grouping needle-sticks in 1 – 2 specific areas weakens the wall producing an aneurysm. In AV fistulas, a less commonly used alternative is the "button-hole" method. With this method, the AV fistula is always punctured through a limited number of sites, that are rotated. The needle must be placed precisely through the same needle tract used previously [57]. Special "dulled" needles are used to minimize laceration of the buttonhole tract. There is no published experience with the buttonhole method in AV grafts.

Anesthesia: In pain-sensitive patients, a topical anesthetic cream can be applied to the skin prior to puncture. Use of local anesthetics (xylocaine) is infrequently used in many dialysis centers although there is no evidence of benefit or harm. There has been no systematic study whether local anesthetics affect the frequency of infiltrations or other complications. It is our observation that in a significant number of patients adequate site rotation is difficult without use of local anesthesia.

Hemostasis: This is achieved by direct pressure following needle removal. One must prevent hematoma at the wall of the access puncture as well as control bleeding at the skin exit site. The 2 puncture sites are not identical because of the oblique path of the needle. Pressure must be held for at least 10 min before checking the needle site for bleeding. Prolonged bleeding > 20 min may indicate increased intra-access pressure and is common in patients on therapeutic doses of warfarin. Adhesive bandages should not be applied until complete hemostasis is achieved.

Complications

Complications related to vascular access are a common reason for hospitalization in chronic dialysis patients. The USRDS reports that access failure (usually due to thrombosis) is the most frequent cause for hospitalization. In some centers, access complications accounts for the largest number of hospital days in ESRD patients [58].

Poor flow: Intra-access flow inadequate to meet that prescribed leads to access recirculation, decreasing dialysis efficiency. In autologous native fistulas, access recirculation can at times be detected by sequential monitoring of the urea reduction ratio (URR) or *Kt/V* and looking for signs of underdialysis. A common sign of inadequate access flow is excessive negative pressures at the arterial needle [59]. Stenosis distal to the usual placement of the needle will produce, in the absence of collaterals, a high venous resistance. The most common cause of poor flow with AV fistulas is a fibrotic stenosis/stricture *within* the venous limb resulting from improper site rotation or infiltrations. Because poor flow eventuates in thrombosis, early detection and treatment may salvage the fistula. Injection of angiographic dye into the fistula (fistulogram) can often locate the obstructed area and angioplasty can correct the stenosis. At times, a surgical revision using a bypass graft is needed.

Unlike the situation in AV fistulas, a flow low enough to produce chemical abnormalities in URR, *Kt/V*, or in the measurement of recirculation percentage as premonitory signs of impending access failure is the exception rather than the rule [60]. Most problems arise from venous outlet stenosis that is heralded by increases in intra-access pressure fistula.

Stenosis: Over 85% of AV graft thromboses are associated with a hemodynamically significant stenosis. Stenoses arise from intimal

fibromuscular hyperplasia [61] usually at or within several cm of the venous anastamosis [62]. There is no way of preventing this process at present. Numerous trials in the coronary circulation using a variety of pharmacologic agents including fish oil, antiplatelet drugs, anticoagulants, corticosteroids, and calcium channel blockers to prevent vascular restenosis have shown no effect on frequency nor severity of the process. In vascular accesses for HD the experience is similar [63] although less extensive [64]. The most active area of current research is the evaluation of intraluminal radiation (brachytherapy) following angioplasty. Gamma irradiation affects self-renewing tissues by arresting cell-division and blunting local cytokine release.

In autologous AV fistulas, the cause of stenosis tends to be more varied, and may be due to turbulence, pseudoaneurysm formation, and needle-stick injury. Early detection permits correction of stenosis (by angioplasty or surgical revision) prior to thrombosis and extends the useful life of the access. Monitoring of vascular access for stenosis also helps maintain adequate blood flow to prevent underdialysis.

Thrombosis: In AV fistulas, occurrence of thrombosis occurs bimodaly, occurring either soon after construction or as a late event. Early thrombosis results from technical factors, maturation failure, or inadvertent compression while sleeping and necessitates surgical correction. Poor flow precedes late thrombosis in most cases, but may be precipitated by hypotension or hypercoagulability. Treatment of thrombosis is difficult. Neither surgical nor percutaneous methods using urokinase provide good results. The recent development of atherectomy and hydrodynamic thrombectomy devices increase the likelihood of salvaging thrombosed AV fistulas. Technical success varies inversely with occlusion time [65]. Thus it is advisable to intervene as early as possible after thrombosis occurs. Salvage of the access should be attempted if the fistulogram demonstrates a correctable site of obstruction in the venous limb after declotting.

In synthetic AV grafts, thrombosis can be managed by surgical thrombectomy or by mechanical or pharmacomechanical thrombolysis. The expertise of the medical center as well as availability of interventionalists frequently determines the choice. However, it is essential that the following be considered:

- treatment performed within 48 hours to avoid the need for femoral vein or other central vein catherization for dialysis;
- access evaluation post declotting with fistulography to detect residual stenosis [66]; and
- residual stenosis corrected with balloon angioplasty or surgical revision.

Early thrombosis after initial technical success is rather frequent after percutaneous treatment or simple surgical thrombectomy. Patients who clot with intra-access flows greater than 1000 mL/min should be educated about avoiding the application of excessive pressure to their accesses, worked up for hypercoagulability, and/or monitored for delayed hypotension. They should be taught how to avoid excessive pressure over the needle sites following dialysis and to check their access for patency several times each day. The role of antiplatelet drugs or warfarin in patients with recurrent thrombosis is unknown. There are no prospective, randomized studies demonstrating a beneficial effect of vitamin K antagonists in preventing graft thrombosis. Similarly no single trial of aspirin, alone or in combination with dipyridamole, has unequivocally demonstrated reduction in access thrombosis [67]. Newer agents that block ADP, thrombin, serotonin, and PAF-induced platelet aggregation hold promise since these mediators are more likely to be generated at

or accumulate at sites of endothelial injury and vascular stenosis. Prospective clinical studies are needed to prove clinical effectiveness in preventing access thrombosis.

Ischemia in the access extremity: Ischemia distal to an AV access can occur at any time varying from hours to several months following access construction. Mild ischemia is manifested by coldness or parasthesias but in the absence of sensory or motor loss, it can be managed expectantly. Pain in the hand on exercise or in extreme instances occurring at rest, a "steal" effect, or the development of non-healing ulcers in the access extremity are indications for surgical intervention. Severe ischemia with nerve injury is an emergency.

With the usual radiocephalic side-to-side fistula, the radial artery anastomosis regularly steals blood flow from the ulnar artery system. Converting the side-of-artery to an end-of-artery anastomosis can sometimes treat ischemia due to steal. The risk factors for steal are the same for AV fistulas and synthetic grafts. Patients with DM, older persons with atherosclerosis, and those with vascular anomalies are at greatest risk. However, because the access flow increases rapidly and is maximal within days of constructions with an AV graft, the symptoms can develop more rapidly and the danger of permanent nerve damage is greater than with a native fistula. Cholesterol embolic events to the fingers can occur with AV grafts necessitating surgical ligation of the graft. Even though the embolic source is not corrected, the decrease in shear stress from a 10-fold reduction in flow reduces the likelihood of continued embolization form the ulcerated plaque.

Edema of the hand: This results from increased pressures in the veins draining the hand. With a native wrist fistula, treatment is by converting the anastomosis from a side-of-vein to an end-of-vein opening or by selectively tying off affected veins in the hand. A small increase in circumference (2 – 3 cm) of the forearm or arm bearing the access is common particularly when the access is constructed above the elbow since, even with a well functioning access, venous pressure increases in the draining veins due to the large increase in flow. Larger pressure increases indicate venous hypertension due to venous outlet stenosis. In native fistulas these occur within 5 – 6 cm of the AV anastamosis and frequently at venous valves. In grafts, the stenosis typically is within 2 – 3 cm of the venous anastamosis. Stenosis also results from previous use of central vein catheters on the same side as the access.

Pseudoaneurysms and aneurysms: In AV fistulas, pseudoaneurysm of the venous limb is much more common than a true aneurysm. In both fistulas and grafts, pseudoaneurysms occur from the lack of proper needle site-rotation as well as from inadequate hemostasis with extravasation of blood following dialysis needle removal. Both kinds of aneurysms are treated by simple observation and by avoiding needle insertions near the aneurysmal site. Large lesions can prevent adequate needle placement and thus limit potential puncture sites. Marked enlargement may compromise the integrity of the overlying skin leading to hemorrhage from aneurysm rupture. Aneurysms that are rapidly expanding or threaten the viability of the overlying skin should be treated by resection and insertion of an interposition graft. In grafts, expansion to a size > 12 mm in diameter is also an indication for correction.

Infections: In AV fistulas, infections are rare and usually staphylococcal in origin. The overall frequency of infection is < 1% over the entire life span of the fistula. Diagnosis is based on local signs of inflammation. Prompt therapy with anti-staphylococcal antimicrobials after local and blood cultures have been obtained is often curative. Duration of therapy

is the same as for bacterial endocarditis. Only septic emboli during therapy warrant removal of the fistula.

Infection in grafts is more common, occurring in 5 – 20% of grafts placed. Thigh grafts have a higher rate of infection than upper extremity grafts because of the differences in hygiene. Prophylactic antimicrobials should be used when HD patients with vascular grafts undergo procedures capable of inducing bacteremia such as dental extraction, genitourinary manipulation, colonoscopy, or ERCP. Most graft infections are staphylococcal, but gram-negative organisms such as *Escherichia coli* may be occasionally cultured, particularly if the access is in the thigh. Initial antibiotic coverage should include gram-negative and -positive organisms as well as *Enterococcus*. Local infection of a graft can be treated with antibiotics based on culture results and by incision/resection of the infected portion. Extensive graft infection requires complete excisional removal. Hemorrhage may occur due to rupture of an infected graft. A graft placed within 30 days that has become infected should always be removed.

Septicemia may occur without local signs. A technetium- or indium-labeled leukocyte scan may help reveal a graft infection, but care must be taken to remove any blood soaked dressings prior to scanning, as they may lead to a falsely positive result. As discussed by Schwab et al [1997], prophylactic antibiotics should be used (cefazolin or vancomycin) to minimize the risk of access infection when the access is surgically manipulated or placed [68].

Congestive heart failure (CHF): Blood flow rate through a fistula or graft can vary from barely adequate (400 mL/min) to over 2000 mL/min. Wrist fistulas have lower flows than elbow level fistulas. Similarly, graft accesses constructed in the forearm have lower flows than those placed in the arm since the brachial artery provides a larger diameter vessel than does the radial artery. Thigh grafts are sometimes constructed with an arterial taper or banding to avoid very high flows. CHF is unusual with a wrist fistula or forearm graft but may occur in patients with arm or femoral access. Surgical narrowing or banding should be done only after cardiac studies have shown marked changes in cardiac output following transient occlusion of the fistula. Long-term cardiac function is generally unaffected by the presence of a fistula. High cardiac output can also be seen in patients who are severely anemic or receiving direct vasodilators and are not on a beta blocker.

Early Detection and Treatment of Vascular Access Malfunction

AV access thromboses are associated with a hemodynamically significant stenosis in most cases. Early detection permits correction of stenosis prior to thrombosis and extends the useful life of the access. Intervention with percutaneous transluminal balloon catheter angioplasty (PTA) or surgical revision to correct stenosis before thrombosis occurs dramatically reduces thrombosis rates and the loss of AV grafts [69 – 71]. Maintenance of access patency depends on blood flow but the threshold values below which the risk of thrombosis increases depends on the type of access. The usual flow through a native wrist AV fistula averages 500 – 800 mL/min whereas in upper extremity grafts the flow is higher, typically > 1000 mL/min with occasional patients having flows as high as 3L/min. In our experience, autologous AV

fistula may maintain patency at flows as low as 200 mL/min. By contrast, the risk for thrombosis in AV grafts begin at access flows between 600 – 800 mL/min [72, 73], flows that provide adequate dialysis but offer few clinical premonitory signs that the access is at risk for thrombosis. Therefore, monitoring of vascular access for stenosis has 2 primary goals: maintenance of adequate blood flow to prevent underdialysis, and prevention of thrombosis.

Stenoses detected by a monitoring program can be treated electively by surgery or angioplasty to decrease the risk of clotting and loss of the access site. PTA can be used to open stenoses at anastomotic sites, within arteriovenous grafts, in the main veins of a native arteriovenous fistula, or in the subclavian vein draining the access arm [74]. Lesions not amenable or resistant to angioplasty can be corrected with an atherectomy device [75], a stent [76], or by surgical revision [77].

The most common cause of stenosis in AV grafts is myointimal hyperplasia, which usually occurs at or just distal to the graft-vein anastomosis. Myointimal hyperplasia occurs whenever there is injury and is a stereotypic response. Vascular smooth muscle cells (VSMCs) proliferate and migrate from the media into the intima. The process probably starts with increased basis fibroblast growth factor (bFGF) released by damaged VSMCs followed by local expression of platelet-derived growth factor (PDGF) originating from platelets, macrophages, and smooth muscle. A portion of VSMCs rapidly enters a replicative cell cycle within 48 hours and this cohort continues to proliferate. Since injury is induced by all procedures that correct the stenosis, it is clear that stenosis is likely to recur. Frequently after angioplasty, the degree of late loss of luminal cross sectional area appears to be proportional to the amount acutely gained. Understanding and controlling the injury process may permit better results following angioplasty. Clearly, the long-term solution requires direct inhibitors of the stenotic process [61] Until then, accesses should be monitored to detect dysfunction.

Risk factors for thrombosis: The risk of thrombosis is dependent on access flow and access type as previously discussed. Native AV fistulas frequently maintain patency at flows as low as 200 mL/min whereas AV grafts thrombose at access flows between 600 – 800 mL/min. The risk of access failure is higher in patients with severe vascular endothelial disease, a useful marker of which is high plasma thrombomodulin [78]. A variety of other comorbid conditions such as DM, hypotension, hypoalbuminemia, anticardiolipin antibodies, hyperhomocysteinemia, and increased serum lipoprotein (a) levels increase thrombosis risk [79]. For primary fistulae, development of stenosis during a 2 year cross-sectional study in non-diabetic patients correlated with higher serum levels of monocyte chemoattractant protein B1 and interluekin-6, cytokines that regulate VSMC proliferation [80]. Patients who developed stenoses in native fistula also had hyperinsulinemia, hyperlipidemia, and increased plasma levels of plasminogen activator inhibitor, factors that affect VSMC function.

Clinical indicators of stenosis: Recurrent clotting (defined as more than one episode/month), difficult needle placement (usually due to strictures), difficulty with attaining hemostasis (within 20 min of needle withdrawal and usually due to intra-access hypertension), and a persistently swollen arm, all suggest that a stenosis is present. These as well as the usual indicators of underdialysis (reduced URR and *Kt/V*) are generally late manifestations of access dysfunction.

Despite the limitations of physical examination, it should be performed at monthly intervals particularly in programs without

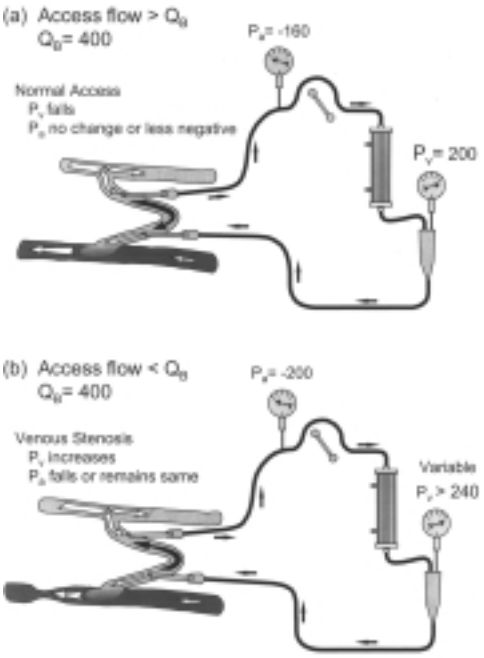

Figure 1. "Poor man's" test for recirculation using compression between the needles. The top panel depicts a well functioning access without stenosis. Access flow is sufficient to meet blood pump demand. With 15-gauge needles, pre-pump pressures are > –220 mmHg and venous drip chamber pressure is < 250 mmHg. Bottom panel depict the effect of venous outlet stenosis with access flow decreased to less than pre-pump. Under these conditions, access recirculation is obligatory. Compression of the access between the venous and arterial needle eliminates the recirculation and forces all of the flow to exit through the venous outlet. As a result the venous drip chamber pressure increases markedly.

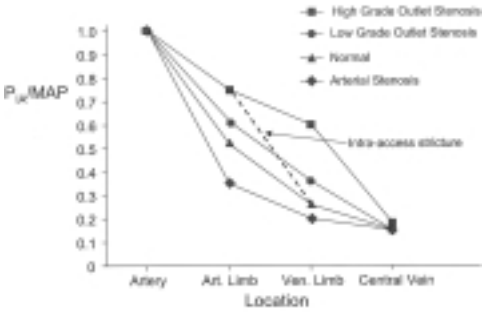

Figure 2. Pressure profiles within prosthetic graft vascular accesses. In a well-functioning graft access, pressure decreases to one-half of mean arterial pressure at the arterial segment and to one third of mean arterial pressure at the venous segment. A venous outlet stenosis increases all pressures proximal to the lesion. A stenosis in the body of the graft between the needles elevates only the arterial limb pressure. An arterial segment stenosis lowers all pressures. By contrast, native fistulas (not shown) have low pressures throughout which typically are unaffected by development of stenosis because of collateral flow.

other monitoring capabilities. A palpable thrill at the arterial, body, and venous segments of an AV graft predicts a flow > 450 mL/min [81]. Loss of the thrill, conversion to a pulse, indicates loss of high turbulent flow. Another sign of low flow in a graft is a discontinuous, water-hammer type of pulse. It has been suggested that a discontinuous, systolic, harsh, high-pitched bruit over the access site is also suggestive of stenosis. This contrasts with the continuous, soft, low-pitched bruit heard over a well-functioning access site [82].

We have found that a simple test as described by Depner will detect critically low access flow when the access flow is less than that demanded by the blood pump, that is when access recirculation is occurring [83]. If gentle occlusion of the graft segment between the dialysis needles during dialysis results in a marked rise in venous chamber pressure, then an outflow stenosis is likely (Figure 1a). An increase in the negativity of the pre-pump arterial pressure suggests that arterial inflow is inadequate, usually due to stenosis (Figure 1b.). This simple test is most useful in native AV fistula.

Pressure-flow relationships in vascular accesses and the effect of stenosis: Access flow, intra-access pressure, and resistance are mathematically related. However the axial pressure profiles of grafts and native fistulas differ significantly (Figure 2) when pullback

pressures are performed [84]. In AV fistulas, blood entering the venous system continues its return to the heart via multiple collateral veins. Even when a stenosis develops, a major increase in venous limb intra-access pressures is prevented unless the outflow stenosis is very central (axillary or central veins). Inflow stenosis in AV fistulas also tends to be silent with venous pressure measurements alone.

By contrast, blood entering an AV graft can only exit through the venous outlet and its draining veins. In an AV graft, the intragraft pressure is normally < 50% of the mean arterial pressure (MAP). Most of the arterial pressure is dissipated across the 2 anastomoses (45% arterial and 20% venous) unless an intragraft stenosis is present. When outflow stenosis develops, usually as a result of neointimal hyperplasia in proximity to the graft-vein anastomosis, intragraft pressure rises (Figure 2). The magnitude of rise is proportional to the degree of stenosis. When intragraft pressure rises above 50% of the MAP, a 50% by diameter stenosis is likely.

Blood flow and the risk of thrombosis: Blood flow in an AV fistula increases progressively over the first few months while the access is maturing. Flow through a native AV wrist fistula commonly averages 600 – 1000 mL/min whereas elbow level fistulas can exceed 2 L/min. Blood flow in AV grafts is maximal within 6 weeks of construction, then decreases variably over time among patients. Forearm grafts average about 1L/min, whereas upper extremity grafts flow is somewhat higher and may range up to 3L/min. In cross-sectional and longitudinal follow-up studies of vascular accesses, the pressure-flow profiles of fistulas and grafts differ substantially [85]. Intra-access pressure is independent of flow in native fistulas [85] and native AV fistulas may maintain patency at flows associated with marked recirculation and decreased dialytic efficiency. By contrast, as grafts develop increasing degree of stenosis (sometimes within months), a pressure gradient develops increasing the intra-access pressure and decreasing the flow (Figure 3). If a stenosis develops in the body of the graft between the areas used for arterial and venous limb cannulation, intra-access pressure at the venous needle will remain normal but flow will still decrease. AV grafts begin to thrombose at access flows between 500 – 800 mL/min [72, 73, 85], flows that can provide adequate dialysis but that offer few clinical warning signals or signs that the access is at risk for thrombosis. The likelihood of thrombosis within 6 months increases 4-fold when access flow decreases below 600 – 700 mL/min. Thrombosis rates also increase with the degree of stenoses [73]. The development of stenosis among patients with grafts is highly variable. Some patients develop stenoses within months while others develop no lesions over several years.

Methods to detect accesses at risk for thrombosis: All methods directly or indirectly evaluate access flow. The most useful clinical techniques to screen patients for functionally significant stenotic lesions have been the use recirculation, post-dialyzer venous drip chamber pressures (P_{DC}) at low flows (dynamic pressures), and intra-access pressure (P_{IA}) under no flow (static) conditions. On-line flow measurements are increasingly used. The following considerations must be kept in mind when using any diagnostic test and then planning corrective action for the lesion(s). First, as discussed above, the ability of a test to detect functionally significant stenoses depends on the prevalence of the lesion. Since development of stenosis is common, particularly in grafts, tests which do not achieve sensitivity and specificity of ≥ 80% or better are not useful. No test has perfect accuracy or predictive power. Unfortunately, accuracy of some tests also depends on location of the

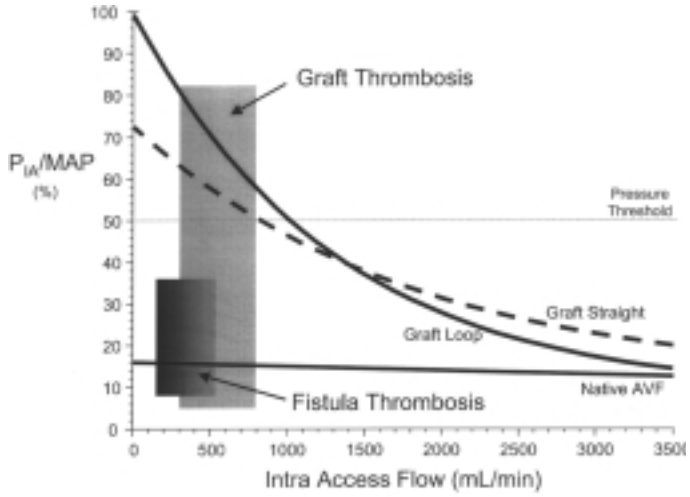

Figure 3. The relationship of intra-access pressure to flow in permanent vascular access. Venous pressure in the access (P_{IA}) is normalized by the mean arterial pressure (MAP). The profiles differ between native fistulae and AV grafts. Normalized intra-access pressure is independent of access flow in native fistulae even with stenosis. In contrast, intra-access pressure increases proximal to the recording venous needle in both loop and straight in AV grafts. Access flows associated with thrombosis in grafts is depicted by the light gray shaded area which extends to the right of usual dialyzer blood flows. Risk of thrombosis in native fistulas is shown by the darker gray shaded area

lesion(s) within the access or its outflow tract. Second a test should be able to detect the lesion before it proceeds to thrombosis. Therefore, it is important that the lesion be detected when its severity is moderate (i.e. degree of luminal reduction that is < 70%), so that there is adequate time to plan non-urgent intervention.

Recirculation

Access recirculation does not develop until access flow decreases to a level equal to or less than that being drawn by the blood pump [60]. Its chemical effect is to produce underdialysis since the return of dialyzed blood to the arterial needle dilutes the blood urea nitrogen (BUN) concentration in the blood going to the dialyzer. As shown in Figure 4, if the brachial artery supplying the access delivers a flow 60 mL/min greater than that demanded by the blood pump, access recirculation will be absent [86]. Thus, barring inadvertent needle reversal or improper needle placement, access recirculation will not be present until access flow falls to the range of 350 – 500 mL/min. By turning down the blood flow, it is always possible to attain a dialysis without recirculation but not one that provides the prescribed dialysis within the prescribed time.

Use of peripheral venous blood for the systemic sample to calculate recirculation overestimates access recirculation substantially because the BUN from this site exceeds that in arterial blood due to AV disequilibrium from cardiopulmonary recirculation and venovenous disequilibrium from regional blood flow inequalities. Recirculation values of ≥ 10% result from these non-access effects and from laboratory measurement imprecision. Patients with CHF can have even greater values (up to 25 – 40%). Access recirculation can be accurately measured by a method in

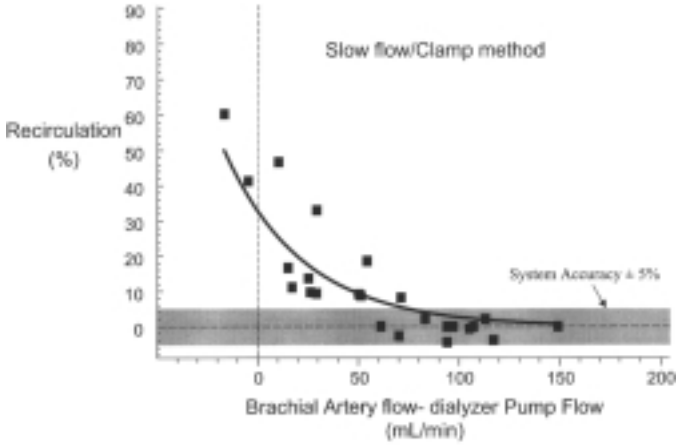

Figure 4. The relationship of the degree of mismatch between arterial artery blood flow supply and dialyzer blood pump demand and the magnitude of access recirculation. The shaded area reflects the accuracy of BUN stop-flow measurements (± 5%). The difference between arterial flow and blood pump flow represents nutrient flow to the extremity. Access recirculation develops when the mismatch increases to the point that nutrient flow is compromised (< 50 mL/min). Adapted from Besarab A, Sherman R. Am J Kid Dis 29: 223 – 229, 1997.

which the peripheral sample is obtained 10 seconds following a sudden reduction in blood pump to a blood flow of 120 mL/min [88]. This method correlates quite well with non-urea based methods for measuring access recirculation. All use an *indicator dilution principle.* A solution (usually saline) is injected into the *venous* return line and a *signal* (a change in temperature, conductivity, ultrasound velocity, or hemoglobin concentration) is detected in the *arterial* line. These non-urea dilution methods show that recirculation is zero (detection limit of 1 – 2%) in the overwhelming majority of patients if the access is properly cannulated [89, 90].

Recirculation is most useful in detecting the failing native vein fistula since patency is likely to be maintained even at flows less than those commonly prescribed (i.e. blood pump flows in the range of 200 – 400 mL/min). Also the benefits of screening AV fistula for access recirculation are not necessarily only to prevent thrombosis, but rather, also to prevent underdialysis. By contrast, the graft with an access blood flow < 600 – 700 mL/min is at risk for thrombosis but since the flow is greater than the prescribed dialyzer blood flow (350 – 500 mL/min) the risk can not be detected when recirculation is used as a screening method. At such graft flow rates, which are still above the usual blood pump settings, access recirculation measurements should still be zero. True recirculation in an AV graft is an urgent indication to study the graft, as the risk of thrombosis at a graft flow rate of 350 – 500 mL/min is quite high. Unfortunately, the majority of HD angioaccesses in the US are grafts; this explains the relative infrequency of abnormal access recirculation measurements in the setting of frequent access thrombosis [90].

Pressure Measurements

Dynamic pressure measurements: The finding of a persistently elevated venous drip chamber pressure (P_{DC}) is a well-accepted

means of screening for the presence of a functionally significant venous stenosis [71]. The measurement is made at low dialyzer blood flow rates (200 – 225 mL/min) due to the recognition that the resistance in the blood lines and venous needle at higher blood flow rates confounds the interpretation of the pressure measurements. However, even at the recommended blood flow rate, the measured venous pressure is still about 4-fold higher than the actual intra-access resulting largely from needle resistance [69]. The pressure that triggers further access evaluation varies significantly with needle gauge as illustrated in Figure 5. The critical value for 14, 15 and 16 gauge needles is 80 – 90, 110 – 120, and > 150 mm Hg, respectively, with the 5 – 10 mm Hg variation for each needle gauge resulting from differences in hematocrit (HCT) between 20 – 35%. The critical value must be exceeded on multiple occasions since partial occlusion of the venous needle orifice can result in high pressures even at low flows.

A baseline should be established when the access is first used (new). The pressure should be measured within the first 2 – 5 min into dialysis and the venous needles must be within the lumen and not partially occluded by the vessel wall. The threshold should be exceeded on 3 consecutive dialysis treatments to be meaningful. Trend analysis is more important than any single value. Stenosis at the venous anastomotic site is suggested by progressive increase in P_{DC}. A lesion within the body of the access will be missed if the lesion is proximal to the venous needle.

Static intra-access pressures (P_{IA}): It is logical that the sensitivity and specificity of pressure measurements is improved if intra-access pressures are used to screen patients rather than the venous drip chamber pressures. Measurement of P_{IA} eliminates flow or the effects of partial occlusion of the needle orifice. Since systemic blood pressure influences intra-access pressure, the utility of intra-access pressure measurements is further refined by using a ratio of intra-access pressure to systemic pressure rather than the intra-access mean arterial pressure alone (MAP) [69]. Indeed, data suggest that measurements of P_{IA}/MAP are superior to venous pressures as a screening modality to detect stenoses in AV grafts [91]. A reproducible observation is that venous outlet stenotic lesions in PTFE grafts are more likely to manifest increased pressures than in native vein fistulas. This results in part from greater compliance in native than in PTFE accesses and in part, as discussed previously, from differences in flow patterns between the 2 types of accesses. In PTFE grafts, blood entering the access must exit through the venous outlet and its draining veins. As outlet stenosis develops, a pressure gradient develops that increases the intra-access pressure. In native fistulae, blood entering the venous system can return through multiple collateral veins proximal to an upstream stenosis, thus preventing a major increase in pressure unless such collateral ves-

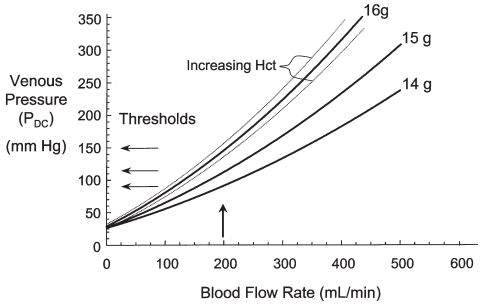

Figure 5. The relationship of venous drip chamber pressure to blood pump flow as a function of hematocrit and needle gauge. Needle gauge is a strong determinant of pressure. At a blood flow of 200 mL/min used for dynamic pressure monitoring, the critical pressure as shown by the horizontal arrows varies from 90 mm Hg for a 14-g needle to 150 mm Hg for a 16-g needle when hematocrits are 30%. A variation in HCT of 5 points around the mean value of 30% produces changes of 5 – 10 mm Hg. Note that at zero flow (static), these influences disappear.

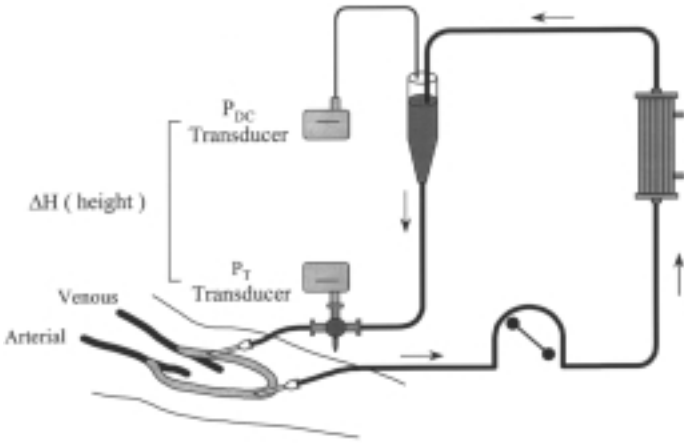

Figure 6. Diagrammatic representation for measuring intra-access pressure. Venous pressure can be measured at the level of the access by a separate transducer system or at the venous drip chamber. Under usual conditions the drip chamber records a pressure less than the separate transducer because of the presence of the hydrostatic column of blood.

sels are absent. As a consequence, pressure measurements appear to be of only modest value as a screening modality in native vein fistulas.

It is impractical to measure intra-access pressures directly. The technique for measuring P_{IA} has evolved to utilize commonly available dialysis equipment [92] rather than a specialized external transducer as is illustrated in Figure 6. When there is no flow, the only difference in pressure between an external transducer and the drip chamber transducer is the difference in height relative to the fistula. Correcting for this offset permits the sequential measurement of an equivalent intra-access pressure ($_{EQ}P_{IA}$) in a prospective way without any special equipment or cost.

The simplified technique for determining $_{EQ}P_{IA}$ uses the pressures from the *venous drip chamber* measured with the blood pump turned off, a "cuff" blood pressure, and an offset. After the blood pump is stopped, a clamp is placed upstream to the venous drip chamber. After 30 – 40 seconds, the pressure in the venous drip chamber stabilizes and is read. This "static" pressure reflects intragraft pressure if the transducer is properly calibrated, but there is the offset: namely, the vertical distance between the top of the blood column in the venous drip chamber and the patient's access. One can measure this vertical distance and correct for it, thereby estimating the intra-access pressure. A value of $_{EQ}P_{IA}$/ MAP > 0.5 is highly specific for a 50% luminal stenosis outlet stenosis in an AV graft.

Flow Measurements

Since a flow < 600 – 800 mL/min in AV grafts is associated with a high risk of subsequent graft thrombosis, flow measurements would be the preferred method of monitoring accesses were it not for associated expense. As mentioned above, pressure measurements indirectly reflect flow and can be used to select patients for referral. However, several "direct" methods of measuring access blood flow are now available. It is reasonable to believe that access flow and recirculation measurements as well as pressure measurements will become routine in the future as these devices are incorporated into dialysis delivery systems.

On line direct measurement of flow: New methods for measuring access flow while on dialysis hold great promise. All of the proposed methods utilize the dilution principle.

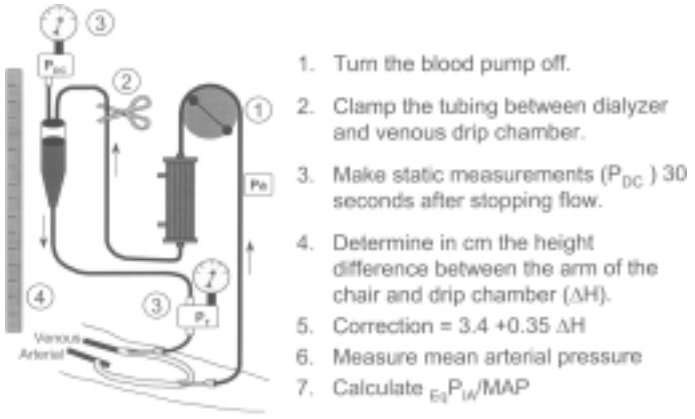

Figure 7. Method for measuring intra-access pressures. The steps are followed in sequence to calculate an equivalent pressure.

Using the method developed by Krivitsky, the blood lines must be reversed as illustrated in Figure 8a so that a signal injected into the venous limb can mix and be diluting by the arterial blood flowing into the access [93]. The blood pump must be stopped sometime during dialysis and the bloodlines transiently reversed in order to perform this measurement. Reversal of the access lines produces an obligatory "recirculation" through the access when the pump is restarted (Figure 8). The percent recirculation that occurs is dependent on the ratio of the blood pump flow rate to the access blood flow rate. This percent recirculation is determined by the injection of saline into the venous line that returns to the upstream position. Once the percent "recirculation" under such reversed line conditions is measured, the access blood flow is calculated algebraically because the blood pump flow rate is known

(Access flow = Blood pump flow [(1 – R)/R]; R = recirculation).

The most accurate results are obtained if 2 detectors are used, one to measure the magnitude of the original signal and one in the arterial line to measure the degree of dilution (Figure 8b). The sensors can also be used to calibrate the pump.

These methods are able to measure access recirculation, access flow, and cardiac output during dialysis. Ultrasound dilution measurement of flow velocity has been evaluated most thoroughly to date and appears accurate and easy to use. However, methods that use and can detect changes in conductivity, hemoglobin, or thermal energy are feasible. The signal does not need to be a bolus of saline into the bloodlines. One method suddenly increases the dialyzer ultrafiltration rate thereby increasing the HCT exiting the upstream bloodline. Another method changes the dialysate temperature cooling the blood entering the access from the upstream bloodline. In still another variation of the theme, concentrated saline is infused into the upstream bloodline. The principle remains the same: the extent of the perturbation in the upstream bloodline that is detected in the downstream bloodline depends on the ratio of blood pump to access flow rates.

Doppler ultrasound This noninvasive technique allows imaging of flow through AV grafts and fistulas. A variety of machines are used with differing algorithms for calculating flow velocity. Certain machines systematically underestimate and overestimate flow [94]. Flow measurement by Doppler depends on accurate measurement of velocity and ves-

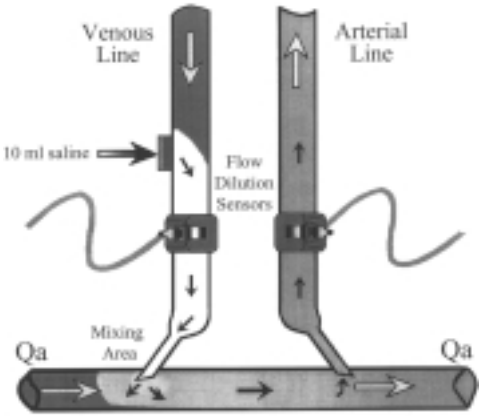

Figure 8a.

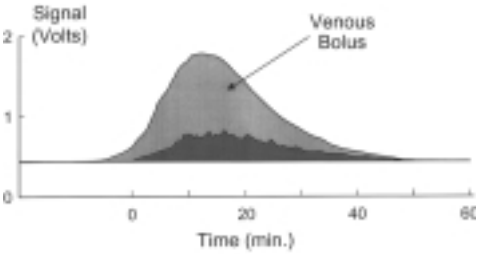

Figure 8b. Method of measuring access flow using the method of Krivitsky. The venous return is placed upstream and the arterial supply to the dialyzer is placed downstream (panel A). As a consequence obligatory recirculation occurs. Arterial inflow mixes with the blood flow returning from the dialyzer. When saline is injected into the venous line it produces a reference signal (area under the curve) for ultrasound velocity of plasma (panel B). After mixing, the arterial sensor measures a lower signal because the mixing dilutes the original signal. Arterial inflow is then derived algebraically.

sel diameter, difficult when flow is turbulent in an access. In such cases, flow is better measured at the brachial artery, where the vessel is a smooth cylinder and where flow is less turbulent. Since all but 60 – 80 mL/min of nutrient flow in the brachial artery flows into the vascular access, brachial artery flow correlates very well with access flow rate [86]. Since lesions can develop within 2 – 3 months of construction or intervention, Doppler flow measurements are prohibitively expensive for routine assessment.

Magnetic resonance angiography: This technique measures access flow quite accurately but is too expensive for routine use.

Imaging the Vascular Access

Ultrasound Imaging: This radiologic method has been useful in the detection of stenoses, and characterization of aneurysms [95, 96]. Its chief role is in the evaluation of flow and anatomy in accesses screened by other techniques. Some centers refer patients with a high probability of stenosis as determined by low cost methods directly for angiography and balloon angioplasty.

Digital subtraction angiography (DSA): Contrast angiography (fistulography) with reflux into the arterial anastamosis (BP cuff inflated) is the gold standard in evaluating the luminal anatomy of the access and its venous runoff systems. Immediate correction of any detected venous stenoses by percutaneous transluminal angioplasty (PTA) can follow the fistulogram. Because visualization of the arterial inflow is often suboptimal by fistulography, intravenous DSA is preferred by some as it provides excellent images of the arterial inflow and distal venous drainage.

Treatment of Stenosis

Percutaneous transluminal angioplasty vs. surgery: A percutaneous technique via a 16-gauge dialysis needle inserted into the graft is used for angioplasty. PTA or surgical revision to correct stenosis before thrombosis occurs. Such interventions dramatically reduce thrombosis rates and the loss of AV grafts [69,

70]. Successful angioplasty or surgical revision should be accompanied by a decrease in either dynamic (blood pump running) or static (blood pump off) access pressures into the "normal" range. Flow usually doubles. Restenosis over a period of 3 – 12 months is a frequent event. PTA yields 90-day patency of 30 – 40% but the procedure can be repeated many times [66, 97 – 99]. Surgical revision provides longer patency but utilizes veins [100]. Subclavian restenosis rate is considerably higher, with only 30% of treated subclavian veins functional at 6 months. Stents may have a role in a small subgroup with elastic stenoses or rapid recurrence.

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Access for Peritoneal Dialysis

Cosme Cruz

Introduction

The peritoneal dialysis (PD) catheter is as important to the establishment and maintenance of PD as the vascular access is for hemodialysis. Thus one of the primary objectives of a PD program should be the organization of a peritoneal access service geared to the implantation and maintenance of adequately functioning catheters in order to optimize the therapy and prolong this dialysis technique survival. Table 1 lists the characteristics of the ideal peritoneal access.

Historical Perspective

Clinical research in PD led to experimentation with PD catheters as early as 1923 [1] with at that time seemingly ingenious means to instill and drain the dialysis solution from the abdomen [2 – 5]. Yet for many years PD access devices were plagued by 2 main problems which prevented the utilization of PD on a wider scale: obstruction caused by debris, fibrin or the apposition of intra-abdominal structures to the catheter orifice; and infection resulting from bacteria entering the peritoneal space not only via the catheter lumen but also along the catheter tract or the resulting cutaneo-peritoneal fistula.

Table 1. Characteristics of Ideal Peritoneal Access.

- Biocompatability
- Resistance to bacteria
- Allows the abdominal wall to function normally
- Easily implantable/removable
- Will not migrate
- Allows for adequate flow without discomfort
- Requires minimal or no maintenance
- Has an integral adapter
- Can adept to any system/cycler used
- Is cosmetically acceptable to patients

These problems continued unsolved until the 1960's when Palmer and Quinton created the first modern PD catheter [6]. This consisted of a tubular structure of silicone rubber with multiple perforations in the distal segment which demonstrated better hydraulic function than previously used devices and with a low incidence of obstruction.

Tenckhoff and Schechter [7], who in 1968 published excellent long-term results on patients treated with PD with a remarkably low incidence of infectious complications improved upon this catheter. Their methods included, in addition to closed systems and meticulous handling of the connections and disconnections (2 fundamental elements in techniques used now) the use of Quinton and Palmer's catheter with 2 important refinements: the distal segment was elongated and coiled to further improve its hydraulic function and Dacron velour cuffs were placed in its midsection separated by 10 cm. The Dacron velour cuffs lead a dual function: they provide structural support by the abdominal

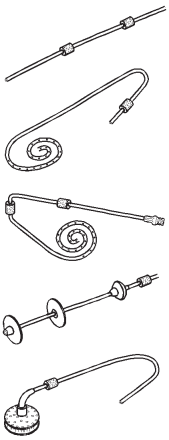

Table 2. Specifications, Materials, and Design of Standard (Tenckhoff) and Newer Catheters.

Catheter	Material	No. of cuffs	Cuff material	Segment between cuffs	Intra-abdominal segment	Additional features
Teckhoff	Silicone (ID = 2.70)	2	Dacron	Generally straight	Straight or coiled	———
Missouri Swan neck	Silicone (ID = 2.70)	1 – 2	Dacron	Arcuate 150° – 170°	Straight or coiled	Pre-peritoneal flange
Cruz	Tecoflex (ID = 3.25)	1 – 2	Dacron	“Pail handle” (two 90° angels on different planes)	Coiled	Uniform, ratio opaque line; built-in adaptor
Toronto-Western	Silicone (ID = 2.70)	1 – 2	Dacron	Generally straight	Straight	Perpendicular discs on intra abdmimal segment
Column disc	Silicone (ID = 2.70)	2	Dacron	One 90° angle long distal cuff	Flat disc	Column disc apposed to the inner abdomal wall

wall and they elicit tissue in-growth on them from the surrounding structures and thus a barrier to bacteria in the pericatheter space is formed as well as a means to prevent the leakage of dialysate.

The incorporation of these Dacron cuffs was a very important advancement in the evolution of the PD catheter. Up to the present time cuffs of Dacron or a similar material is a universal feature in all catheters in use.

The bioincompatibility of Dacron cuffs is ideal for this use. Dacron cuffs are also featured in other implantable devices, such as vascular catheters for hemodialysis (HD) and ports for chemotherapy.

The Function of the Peritoneal Catheter

The main function of this device is to allow a bi-directional flow of dialysate in a consistent manner without requiring extraordinary effort or causing undue discomfort. This flow of dialysate follow simple physical principles [8]. Whether dialysis exchanges are performed manually, as in the case of continuous ambulatory PD (CAPD), or by means of a cycler, the flow of dialysate occurs without any assistance from pumps as a result of pressure differences in the system plus the effect

of gravity. Nevertheless, the PD catheter does not work in isolation. Its function is dependent on its design specifications, its implantation site and the configuration of the dialysis system employed to do the exchanges (Table 2).

To better understand the function of the PD catheter it is useful to review some basic aspects of catheter design and manufacture. Most catheters in clinical use employ the same basic principle and are elongated, flexible tubes with multiple ports in the distal or intra-abdominal segment. This segment can be straight or coiled. Coiled catheters with larger numbers of ports have better hydraulic function. The greater number of perforations in the coiled distal end decrease the resistance to flow. The ideal location for the distal segment of the catheter is a free, unencumbered space in the pelvic area, though not necessarily the bottom of the pelvis. The peritoneal cavity, although ideally suited for dialysis, is also occupied by other structures including mesentery, omentum, fallopian tubes, and bowel, all of which can cause PD catheter obstruction. The catheter midportion, normally implanted within the wall of the abdomen, features 1 – 2 Dacron velour cuffs. These cuffs elicit a reaction from surrounding tissue. This results in tissue ingrowth with obliteration of the space between the device and tissue, reducing the potential for dialysate leakage. Both the location of the intramural segment and the orientation of the site where the catheter exits the skin affect the long-term functional life of the catheter [9]. The area where the skin, catheter and the environment interface must be structurally sound and stable. As the catheter exits the skin, it becomes subject to gravitational forces contributed to by its own weight. These forces are more pronounced when the subject is active and/or in an upright posture. The catheter exiting the abdominal wall cephalad or laterally is hard to keep immobilized in order to prevent (or minimize) the stress of gravity and/or tugging during dialysis exchanges. For this reason, some catheters are pre-shaped so that in their unstressed configuration they keep both distal and proximal segments oriented caudally [10, 11]; this facilitates the creation of a caudally-placed exit orifice without increasing the risk of translocating the intra-abdominal segment. Catheter translocation often is caused by the catheter trying to return to its “memory shape”.

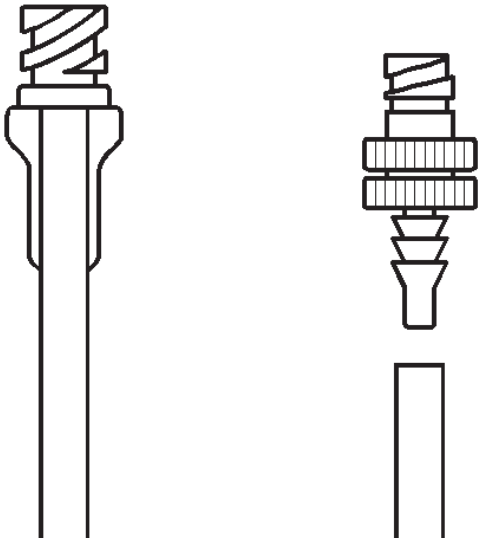

Figure 1. Schematic view of 2 catheters. On the left a catheter with a built-in adapter that preserves the internal diameter throughout. On the right a catheter with a mounted on adapter that creates a stricture at this junction.

The proximal segment of the catheter, which is the visible segment one manipulates during the dialysis exchanges, attaches to the dialysis line by means of an integral adapter or a “mounted-on” adapter (Figure 1). Most mounted-on (conventional) adapters fit inside the catheter distal tip and have smaller lumina, which creates a structure in the dialysate flow path adversely impacting flow rates.

Similarly, the design and specifications of the system employed to perform dialysis ex-

changes influences the function of the catheter. During a typical CAPD exchange the patient sits on a chair with the drain bag on the floor; the bag with fresh dialysate is kept elevated 6 – 7 feet (2 meters) from the floor to maximize the effect of gravity. For this reason the inflow arm of the Y set is longer than the outflow arm. A shorter non-redundant drain line improves outflow time. As stated above, the main functional quality of the PD catheter is its flow capacity. Dialysate flow during dialysis is governed by simple physics principles, as described by the following equation:

$Q = P/R$

where Q = Volume dialysate flow/time, P = Pressure gradient across the end points of the fluid pathway, and R = the hydraulic resistance of the system.

During inflow, the pressure gradient (P) is established by the distance between the top of the column of the dialysate and the distal catheter tip. Conversely, during outflow the P depends on the distance between the intraperitoneal space and the drain bag. As the distance between these points increases, gravity enhances flow velocity. The hydraulic resistance (R) to flow depends largely on the size of the fluid channel. Thus, the design and specifications of the PD sets are major determinants of dialysate flow rates and influence dialysis efficiency.

One can easily manipulate the P/R ratio in order to enhance the flow rate by elevating the dialysate bag maximally during inflow while placing the patient in the supine position (the intra-abdominal pressure is lowest supine and highest sitting). Conversely, during outflow the same is accomplished by lowering the bag maximally and using large capacity drain bags in order to minimize resistance to flow by a filing bag. The pressure gradient changes constantly during the performance of a dialysis exchange, being higher in the early stages of outflow/inflow modes and decreasing as the abdomen and the drain bag fill.

The importance of the PD catheter and dialysis set designs and specifications has been defined only recently. Early studies involving silicone catheters with standard (mounted on) adapter [8] reported dialysate flow rates of 2 – 2.6 mL/sec. The usual time allocated to perform a 2 L exchange was 20 – 30 minutes. The advent of PD catheters made out of polyurethane and featuring larger lumina and built-in adapters with the same internal diameter (ID) [11] has spurred interest by investigators and manufactures in dialysate flow dynamics.

In in vivo studies polyurethane catheters with built-in adapters 0.130 inches in internal diameter have consistently shown superior flow compared with silicone catheters with an ID = 0.108 inches (Table 3) [12].

The Impact of Catheter Design on Clinical Outcomes

As the number of patients on CAPD has increased world wide, access failure has become one of the major causes of technique failure. Problems with catheter migration, outflow obstruction, inadequate hydraulic function and infection of catheter tunnel and exit orifice present a serious challenge to clinical investigators and the industry.

Over the years a plethora of new catheter designs to solve these problems has emerged [13 – 21]. However, time has demonstrated that few designs have proven to be superior to the original Tenckhoff catheter design 3 dec-

Table 3. Dialysate Flow Rate According to Catheter/set Design (mL/sec)

	N	Set A	Set B	% Change	P
		(ID = 0.150 in)	(ID = 0.2–in)		
Outflow					
Silicone catheter (ID = .108 in)	10	4.51 ± 0.32	5.57 ± 0.92	23.5	NS
Polyurethane catheter (ID = .130 in)	11	6.12 ± 0.92	9.68 ± 1.89	58.2	0.001
Inflow					
Silicone catheter (ID = .108 in)	10	6.07 ± 0.42	6.51 ± 0.85	7.2	NS
Polyurethane catheter (ID = .130 in)	11	6.94 ± 0.97	9.45 ± 1.69	36.2	0.001

ades ago. Center catheters although in theory of superior design (or more complex) have created their own complications related to: their implantation, especially if the intra-abdominal segment is voluminous; inadequate flow; difficult removal; and infectious complications. As permanently implanted devices increase in size they become a greater problem when infected [14].

The study of these new catheter designs and their own attending complications has nevertheless resulted in a better understanding of the pathophysiology of percutaneous access and spurred interest in this field of investigation.

Interestingly the realization that simplicity in catheter design is associated with better clinical outcomes has led to the development of catheters which incorporate the fundamental elements of the Tenckhoff catheter albeit with some refinements [8, 9, 13].

Swan neck and Cruz catheters (refinements of Tenckhoff design) offer the additional advantage of allowing the creation of a caudally orientated tunnel and exit orifice while maintaining their material configuration, thus reducing the likelihood of exit site and tunnel infections [9, 10].

Implantation Techniques for PD Catheters

Access adequacy is the result of various factors: the PD catheter, the method of implantation, the expertise of the surgeon, the host's reaction to the device, and the care of post-implantation. In spite of refinements in catheter design and methods of implantation, PD access malfunction continues to be a major cause of this modality's failure [16 – 20]. Catheter implantation always requires some sort of "surgical" procedure. The catheter's design and the patient's surgical history and body habitus dictate the extent of the "surgery". Simple devices can be easily implanted using any number of percutaneous methods [9, 22 – 24]. Complex catheters require a more extensive method involving the incision of the parietal peritoneum. Similarly, an "open" procedure or one of the more sophisticated laparoscopic methods of implantation [9] may be indicated inpatients with previous abdominal surgeries or in the morbidly obese.

Catheter implantation methods have evolved over the years, as it has been the case

in other surgical procedures. Fiberoptic technology and precise instrumentation have reduced the invasiveness of internal or intracavitary manipulations, decreasing patient discomfort while ensuring efficacy. These methods, championed primarily by non-surgeons, are becoming increasingly popular [9, 22 – 24]. The main relative drawback of these methods is their unsuitability for the implantation of voluminous or complex catheter.

Whether a "conventional" surgical method or any of the percutaneous [9, 22, 23] methods of peritoneal access creation is used, there are basic universal principles that apply in terms of patient preparation, surgical techniques, postoperative care, and catheter conditioning prior to its continuous use.

Patient Preparation

Under ideal circumstances, the catheter implantation is planned electively. Prior to the date of the procedure, the patient is given an explanation of it, and his or her questions are answered. At this time, the implantation site is chosen and marked with water-resistant ink. The site of implantation is chosen taking into consideration the presence of scars, the beltline location, skin folds, and preserving the site of a future kidney transplant. On the night prior to the procedure, a laxative is administered to evacuate the bowel. An osmotic preparation produces good results with minimal bowel irritation. This method of bowel cleansing facilitates the intra-abdominal positioning of the catheter and lowers the risk of viscus injury (if a percutaneous approach is used). On the day of the procedure, the patient showers with germicidal soap and empties his/her bladder immediately prior to the procedure.

Antibiotic Prophylaxis

Although there are few prospective studies on the effectiveness of transoperative antibiotic prophylaxis on postcatheter implantation infection, data from other clinical situations involving corporeal access and the implantation of devices [25] suggest a role for a dose of antibiotics administered pre or trans-operatively. One dose of a second generation cephalosporin or vancomycin can be used effectively.

Sedation / Anesthesia

Conventional preoperative sedation with meperidine and midazolam, in standard doses is recommended to increase patient comfort. General anesthesia is not necessary for an uncomplicated implantation, especially if one of the percutaneous methods is being used. An exception to this is the case of video laparoscopy with gas insufflation, which requires the patient to be under general anesthesia. One-percent xylocaine with epinephrine produces good anesthesia and hemostasis on skin and subcutaneous tissue. Plain 1% xylocaine is recommended for the dorsal and ventral fasciae during an "open" surgical procedure.

Surgical Implantation Principles

The Implantation Site: Over the years, a shift from the midline approach in favor of a lateral one (paramedial) has taken place [9, 26]. The advantages of positioning the deep

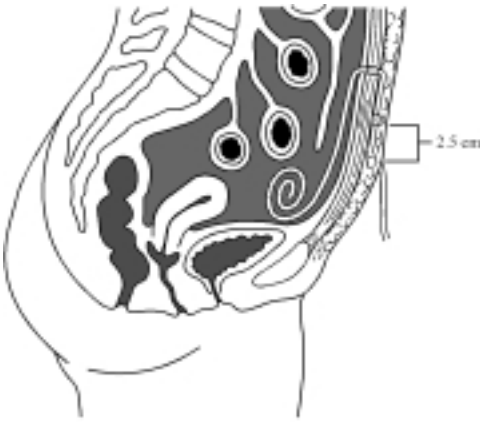

Figure 2. Schematic view of the free position of the PD catheter within the peritoneal space away from the cul de sac. The subcutaneous tunnel is caudally orientated and at least 2.5 cm. Separate the proximal cuff from the exit orifice.

catheter cuff in the body of the rectus abdominal muscle as opposed to the midline are (1) better tissue ingrowth around the cuff due to the richer vascularization of muscular tissue, (2) better structural support for the catheter and, (3) a stronger seal around the catheter, minimizing the risk of dialysate leakage [9, 10]. Regardless of the implantation method used, catheters of simple design ought to be introduced into the peritoneal cavity through a small puncture of the parietal peritoneum. Purse-string sutures around the catheter at the level of the facia prevent accidental dislodgment of the catheter and dialysate leakage [10, 22].

The Placement of the Intra-abdominal Segment: It is important for adequate catheter function that the intra-abdominal segment be free and in its natural, unstressed configuration within the free peritoneal space. A catheter placed in the cul-de-sac not only will cause discomfort during inflow and outflow, but it will be affected by bowel function (Figure 2).

Intraoperative Testing: The testing of the hydraulic function of the catheter prior to the tunneling procedure is of great importance. A 1-L dialysis exchange is performed noting the velocity of dialysate inflow and outflow. An obvious advantage of the use of local anesthesia and sedation over general anesthesia is that it allows the patient to tell if the flow of dialysate causes discomfort or pain. Pain, undue discomfort, the awareness of dialysate flow, and less than adequate hydraulic function are indications for catheter repositioning. This is the best time for any necessary adjustment in the placement of the catheter. Catheters that function less than adequately, initially, seldom improve spontaneously – if anything, they get worse. No implantation procedure should be completed without verification of adequate, painless dialysate flow.

The Tunneling Maneuver: Once the catheter has been verified to show optimal function, it is transversed through a subcutaneous tract and emerges at the exit site (an orifice created approximately 2.5 cm from the subcutaneous Dacron cuff). The tunneling is performed using instruments onto which the catheter's proximal segment is connected to minimize tissue trauma as the tunnel is created [10, 22].

The tunneling should be done in a manner that prevents catheter placement in a "stressed" configuration. The caudal orientation of the tunnel places the catheter/skin interface under less stress than if a cephalad or laterally placed tunnel/exit site is created. The catheter will be more stable and less subject to the stresses of gravity and "tugging" of the catheter occurring during repeated catheter handling. Catheters that are permanently bent [10, 11] and dictate the caudal positioning of both the intra-abdominal and proximal segments offer advantages over conventional (straight) catheter, which would have to be tunneled in an unnatural or stressed configuration in order to achieve the same effect. The elimination of the skin at the exit site using a 4 mm punch biopsy helps prevent the invagi-

nation of dermis around the catheter and results in a clean stable exit site. The catheter exit site should be away from skinfolds, so as to be easily accessible.

Surgical Method

The "open" surgical method of catheter implantation is the most commonly used (approximately 80% of catheters are implanted surgically). This method is effective regardless of the catheter design, although, catheters of large volume or complex configurations require to be introduced into the abdominal cavity through an incision in the parietal peritoneum. Otherwise catheters of simple design require a very simple surgical technique illustrated in Figure 3a – 3r.

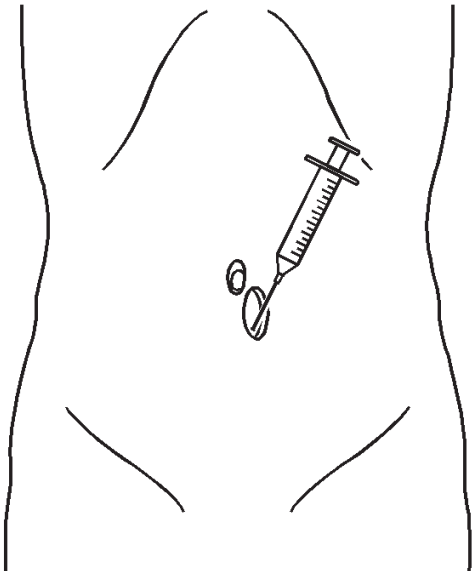

Figure 3a. Surgical technique for a double cuff catheter with built-in adapter. The ideal site of implantation is the paramedial line 2 – 3 cm below the umbilicus. The skin and subcutaneous tissue are infiltrated with 1% xylocaine with epinephrine.

Laparascopic Techniques

Over the last 2 decades alternative methods of catheter implantation have been developed and refined, utilizing simplified laparascopic equipment in order to directly visualize the intraperitoneal space where the catheter is positioned [8, 22, 24]. Typically a trocar – cannula wrapped on a disposal sheet is used as a conduit for the sequential introduction of

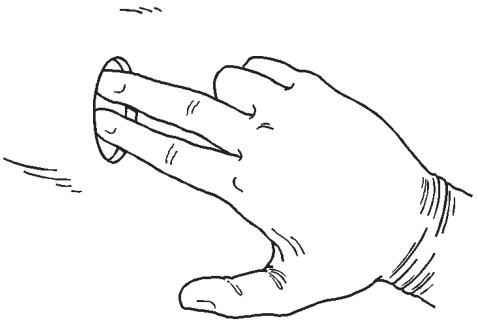

Figure 3b. Surgical technique for a double cuff catheter with built-in adapter. A 5 – 8 cm incision is made as the subcutaneous tissue is dissected with a blunt instrument or electrocautery until the fascia of the anterior rectus muscle is identified.

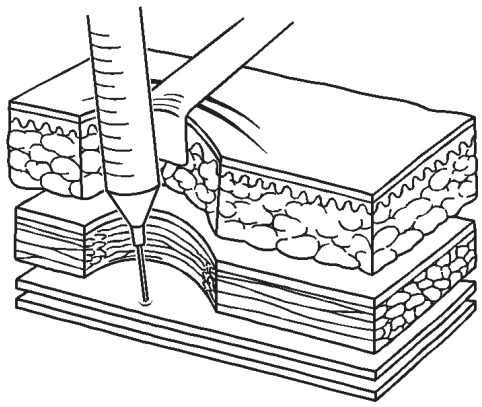

Figure 3c. Surgical technique for a double cuff catheter with built-in adapter. Infiltrate the anterior fascia with 1% xylocaine.

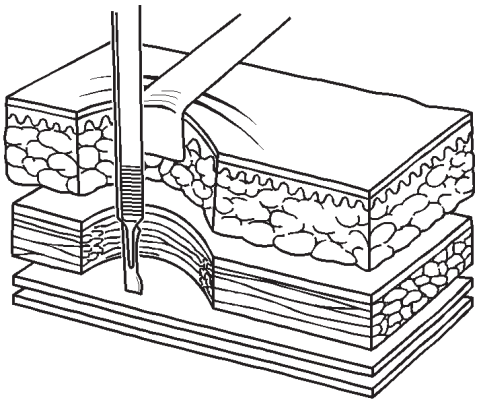

Figure 3d. Surgical technique for a double cuff catheter with built-in adapter. Incise the anterior rectus fascia along the axis of the fibers.

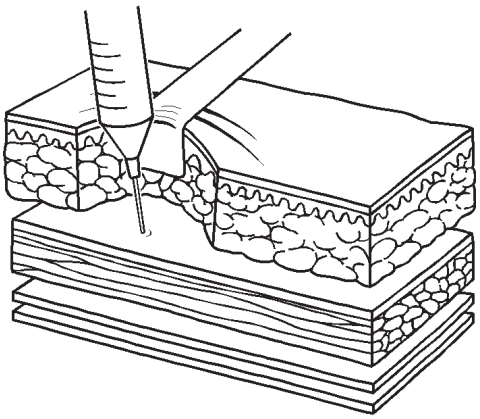

Figure 3f. Surgical technique for a double cuff catheter with built-in adapter. The posterior rectus fascia and parietal peritoneum are then infiltrated with 1% plain xylocaine.

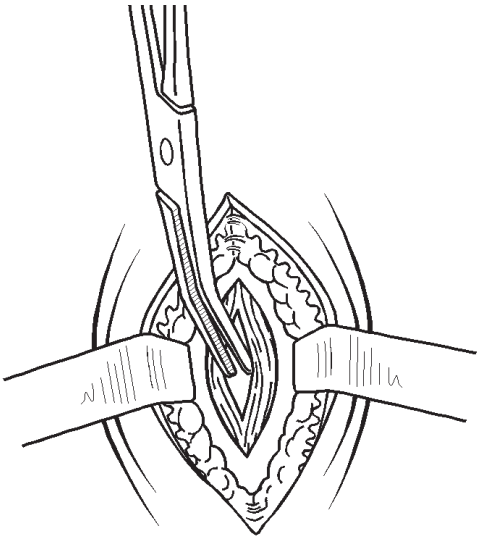

Figure 3e. Surgical technique for a double cuff catheter with built-in adapter. Bluntly separate the rectus muscle fibers along the axis avoiding injury to the epigastric vessels.

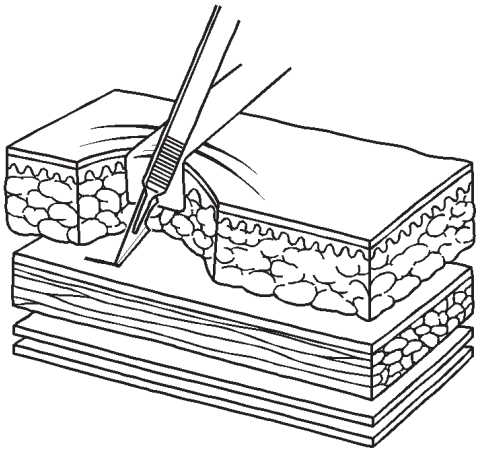

Figure 3g. Surgical technique for a double cuff catheter with built-in adapter. The posterior fascia and parietal peritoneum are then punctured with a number 11 blade or with a muscular clamp to create an orifice through which the catheter can be inserted.

the laparoscope and the catheter into the intraperitoneal space. Compared with the conventional surgical methods simple laparascopic implantation is very effective and less traumatic.

As laparascopic methods are refined this technology has also been employed to manage malfunctioning catheters and to carry out epiplopexy of the greater omentum is cases of obstruction caused by omental wrapping [27].

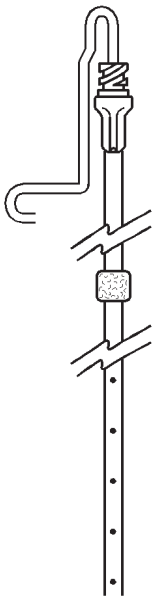

Figure 3h. Surgical technique for a double cuff catheter with built-in adapter. The catheter, which has been soaked in saline and has had the air removed from the cuffs is mounted on a stylet. Be careful that it is not turned on its axis.

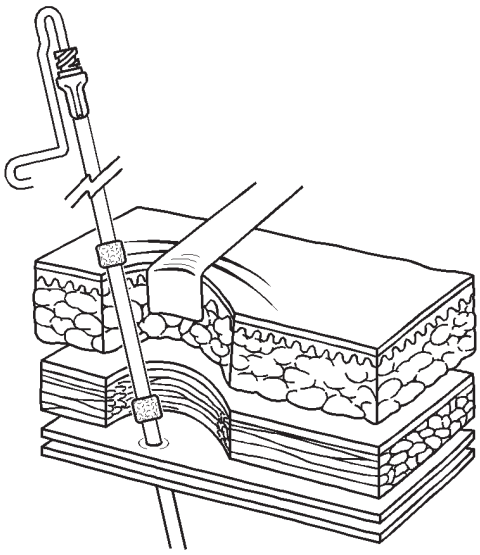

Figure 3i. Surgical technique for a double cuff catheter with built-in adapter. Insert catheter through the peritoneal puncture hole or incision withdrawing the stylet gradually as the catheter advances. The catheter is advanced toward the pelvis.

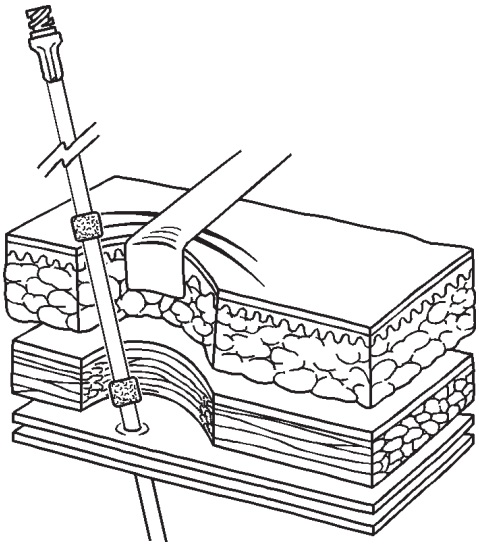

Figure 3j. Surgical technique for a double cuff catheter with built-in adapter. A purse string suture is used to close the peritoneal orifice at the level immediately distal to the distal cuff.

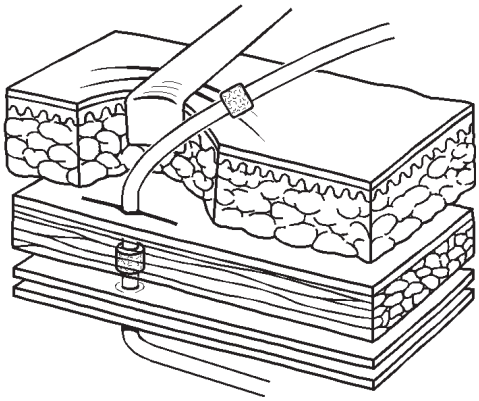

Figure 3k. Surgical technique for a double cuff catheter with built-in adapter. In doing so, the cuff will rest within the body of the rectus abdominal muscle.

Delayed Catheter Exteriorization

This recently introduced catheter implantation method incorporates into an “open” sur-

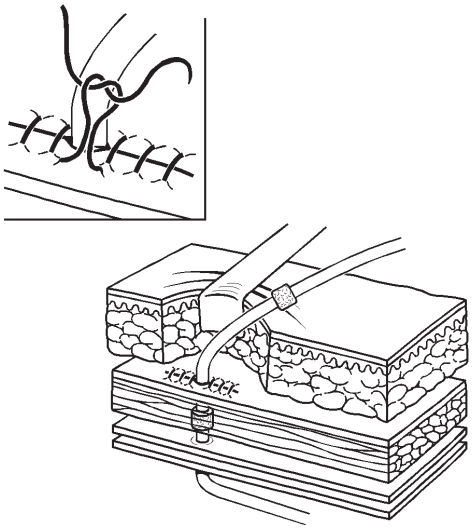

Figure 3l. Surgical technique for a double cuff catheter with built-in adapter. The anterior rectus fascia is then sutured with interrupted absorbable sutures. Once again, care has to be taken that the distal cuff be well within the muscle fibers. A purse string suture using a 0 Vicryl is then made to add security to the catheter. The catheter can now be tested by irrigation with a large syringe and saline solution.

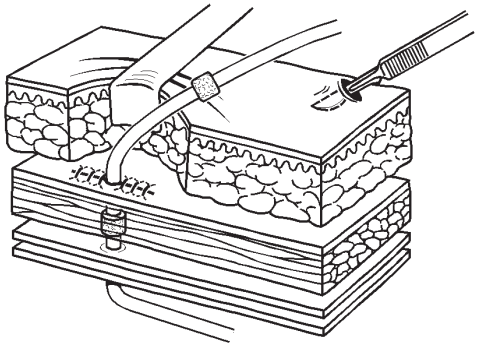

Figure 3m. Surgical technique for a double cuff catheter with built-in adapter. The exit site is preferably 3 – 4 cm away from the subcutaneous cuff. The skin site is anesthetized and a 1.5 – 2 cm stab wound is made toward the primary incision.

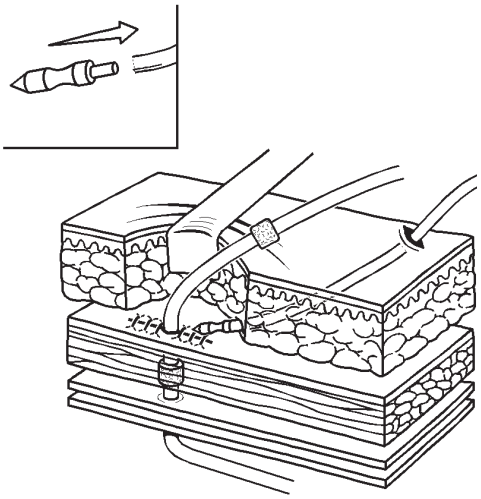

Figure 3n. Surgical technique for a double cuff catheter with built-in adapter. The tunneling device is then advanced through the exit site in the direction of the primary incision.

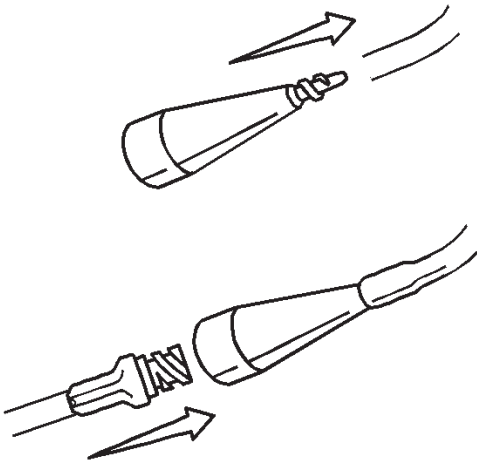

Figure 3o. Surgical technique for a double cuff catheter with built-in adapter. Its tip is removed and replaced by the socket for the catheter adapter.

gical method the positioning or embedding of the catheter external segment in a subcutaneous pouch for a period of 4 – 8 weeks, making a complete wound closure with a secondary creation of an exit site. The aim of this surgical method is the reduction of infectious complication, presumably the result of the introduction of bacteria along the tunnel during the post-operative period before tissue in-growth

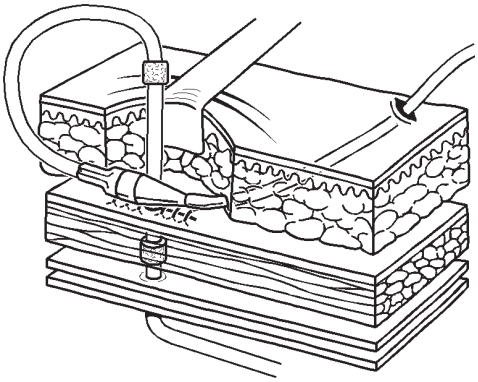

Figure 3p. Surgical technique for a double cuff catheter with built-in adapter. The device and connected catheter are then pulled gently through the exit site in the least traumatic manner.

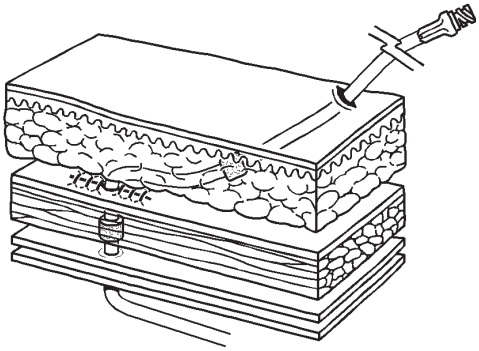

Figure 3q. Surgical technique for a double cuff catheter with built-in adapter. It is recommended to attach an extension set at this time and flush with dialysis or saline solution. The primary incision is sutured in layers.

takes place. By delaying the creation of the exit site, presumably a better bacteriologic barrier between exit site and peritoneum takes place [28]. Some disadvantages of this method have included the inability to initiate or prepare for PD in due time, delayed wound healing, seromas, subcutaneous hematomas, serious obstruction by fibrin thrombi and omental obstruction found at the time of initiation of dialysis [29].

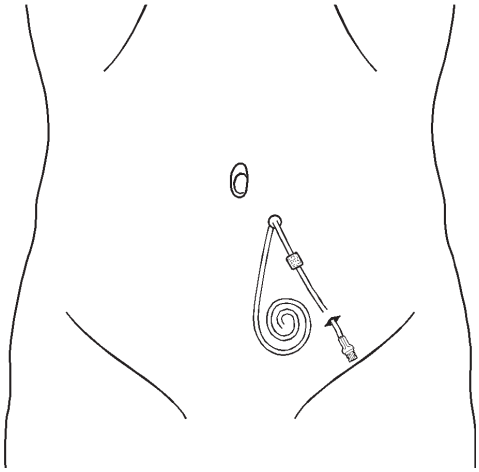

Figure 3r. Surgical technique for a double cuff catheter with built-in adapter. The catheter is now ready for use.

The End Result

Whether an “open” surgical method or any of the laparascopic methods of catheter implantation is chosen, the ideal end result is an efficient unincumbering, easily concealed catheter that functions in harmony with the patient’s peritoneal cavity and the dialysis system chosen. The implanters main aim is thus the creation of a stable interface between catheter, skin and the environment as Figure 3 illustrates.

The Care and Maintenance of the PD Catheter

The care and maintenance of the PD catheter (or lack thereof) are as important as its material design or method of implantation in determining dialysis technique survival.

The maintenance requirements of the PD catheter are largely dependent on its design and the materials used for its manufacture.

The catheters most widely used today feature a permanent bend and a simple (either coiled or straight) intra-abdominal segment. They are manufactured from 2 basic materials, which differ in their physical properties:

Silicone rubber: Silicone catheters have thick walls are thermoset and cannot be bonded to other materials. They have provided adequate function for > 25 years.

Polyurethanes: Polyurethane catheters offer some advantages over silicone catheters in terms of thermoplasticity, tensile strength and their ability to bond to other materials. Thus they can feature a permanently attached adapter. Polyurethane catheters have larger lumina and high flow rates. Polyurethane, however, requires a little extra care as it is negatively affected by high temperatures, certain solvents, such as those contained in the base of topical antibiotic preparation such as mupuricine and prolonged exposure to concentrated chlorinated compounds and hydrogen peroxide [30, 31].

All catheters require basic precautions including the avoidance of using scissors, blades or clamps with either teeth or sharp edges, which may damage the catheter or adapter.

Post-operative Catheter Care

In order to promote would healing and tissue ingrowth on the catheter cuffs so that a bacterial barrier develops, it is recommended that the catheter be immobilized and the wound and exit orifice be covered by a surgical dressing for 3 – 7 days. Thereafter, daily cleansing of the exit orifice with povidone iodine followed by sterile dressing is continued for 6 weeks.

After 6 weeks when catheter implantation should be well established, the exit site care can be reduced to washing with soap and water (while showering) followed by thorough drying (a hair dryer at low setting can be very effective).

From this point on the use of gauze dressing is optional. The preservation of the pericatheter skin integrity is very important and use of the following should be avoided: iodine compounds, alcohol, hydrogen peroxide, adhesives, powers, topical antibiotics, and steroid creams.

Catheter Conditioning

Break-in procedure. The rationale of breaking-in is to maintain catheter patency, especially in the presence of post-surgical bleeding during wound healing and tissue ingrowth between implantation and the onset of dialysis.

Catheters implanted through peritoneal puncture, as opposed to an incision, can generally be utilized following implantation without a break-in period, especially if reinforced by a purse string suture at the level of the distal cuff. However, it is preferable to wait at least 2 weeks to minimize the risk of pericatheter leak.

During this period, patient activity and intra-abdominal pressure should be kept at a minimum, and coughing, lifting and straining while defecating should be avoided.

Flushing Methods

Three main methods may be used for flushing:

– After an initial set of rapid exchanges a two-liter bag of dialysate with 2500 – 5000 units of heparin is connected to the patient followed by infusion of 25 – 50 mL of solution by opening the line every 2 – 3 hours while counting to 5. This small volume of dialysate will clear the catheter of fibrin and blood and will be absorbed by the peritoneal lymphatics. The solution bag can then be replaced every 3 – 4 days by the nursing staff.
– After an initial set of rapid exchanges with heparinized dialysate (2500 µ/L) a rapid exchange is performed every other day in a similar manner leaving 300 – 500 mL in the abdominal cavity each time.
– If the patient is in need of dialysis immediately after the catheter implantation, manual or cycle assisted dialysis can be instituted using small dialysate volumes (1000 mL of heparinized dialysate) during 48 – 72 hours while the patient remains recumbent. Either of the above protocols can then be resumed.

Care of the Catheter/Adaptor Junction

Catheters mounted in conventional adapters often show wear and tear of their end at the adapter site resulting in fissures, leaks and accidental disconnections when they become incompetent. The use of extension segments that can be replaced every few months if damaged by clamps, accidental clipping or cutting, is recommended to prolong the life of the catheter.

Catheter-related Complications

Most mechanical or non-infectious complications can be avoided or minimized with proper implantation technique and catheter maintenance in combination with a judicious dialysis regime.

Immediate post-operative hemoperitoneum, dialysate leakage and catheter obstruction are prime examples of improper surgical technique. The risk of herniation can be substantially decreased by avoiding the use of large volume exchanges in favor of more frequent exchanges of lesser volume. Large intraperitoneal volumes should be only employed when the patient is in the supine position. To this effect the combination of cycler dialysis at night and small diurnal manual exchanges is ideal. Patients should refrain from activities that greatly increases the intra-abdominal pressure such as vigorous exercise or weight lifting. Physical fitness and any method that increases that strength of abdominal musculature should be encouraged. If patients are keen on vigorous training, they can be taught to exercise with a near-empty abdomen.

Care of Catheter-related Complications

Dialysate Leakage

Dialysate leakage through the space between the catheter and the abdominal wall occurs more often if the parietal peritoneum was incised during the catheter implantation,

or when there is failure of the tissue surrounding the distal cuff to grow into it. The incomplete obliteration of this pericatheter space by tissue ingrowth coupled with sudden increase in the intraabdominal pressure causes the dialysate to leak through the tunnel either externally or through the preperitoneal space into the subcutaneous tissue of the abdominal wall, the scrotum in the male or the labia in the female. Delayed wound healing caused by malnutrition or treatment with corticosteroids may predispose some patients to this complication.

Dialysate leakage tends to occur early in the postoperative period. Failure to place a purse string suture around the catheter as it exits the rectus fascia may also cause this complication. Occasionally patients with severe bouts of coughing or who experience sustained elevation of intra-abdominal pressure, as in weight lifting, may experience dialysate leakage.

Rarely dialysate leakage occurs through other weak points in the abdominal wall such as sites of previous laparoscopic procedures, surgical wounds or previous catheter implantation sites and in this instance surgical repairs of the abdominal wall may be necessary. Otherwise, for early postoperative leakage the management includes discontinuation of PD, generally for 3 – 4 weeks or as long as its takes for the pericatheter space to obliterate. During this period the patient should be placed on HD. In extreme situations where HD is not possible cycler-assisted dialysis can be instituted using small volume exchanges while the patient remains in the recumbent position.

Regular dialysis can be instituted when the patient can ambulate for 4 hours with at least 1L dialysate in the abdomen without experiencing leakage.

Catheter Cuff Erosion / Extrusion

This late catheter complication is most often the result of a combination of factors: improper position of the proximal cuff (less than 2.5 cm away from the exit orifice), the effects of tugging on the catheter during the dialysis exchanges and patient weight loss with a decrease in the thickness of the subcutaneous tissue around the catheter. Patients generally note increasing irritation and pain at the exit site with the gradual emergence of the catheter cuff through the exit orifice. Once this problem is identified, the elective shaving of the cuff using a number 11 surgical blade, sterile technique, and one dose of prophylactic antibiotics can salvage the catheter if no other problems are present such as infection of the catheter tunnel. Following the shaving, liquid silicone can be used to coat the site where the cuff was before the positioning the catheter in its usual space.

Catheter Obstruction by Fibrin Thrombi

This complication occurs most often in the early postoperative period particularly if bleeding occurs during the implantation and failure to irrigate the catheter on a regular basis before its continued use.

Catheter obstruction caused by debris or coagulation of transudate can occur also if the abdominal cavity is left dry following the implantation, as occurs with the method of delayed exteriorization of catheters [29]. Vigorous manual irrigation using a large syringe usually solves the problem. In more stubborn

cases the instillation of urokinase can correct the problem: using sterile technique, the catheter is attached to a line through which 10,000 units in 100 mL of saline solution are dripped over one hour. After 1 – 2 hours the manual irrigation can be tried again. Rarely severe obstruction of catheter fibrin can be refractory to all maneuvers forcing catheter replacement.

Catheter Obstruction by Omentum Wrapping

The catheter as a foreign body is often entrapped by omental tissue causing it to obstruct. On rare occasions other intra-abdominal structures can obstruct the catheter such as the appendix and fallopian tubes [32 – 34]. This complication can occur early or late and has a typical presentation characterized by a variable period (weeks, months or years) of adequate hydraulic functions followed by increasing signs of flow restriction especially during outflow until there is total cessation of flow. This process can occur over days or even weeks and is refractory to all irrigating maneuvers and the use of heparin and/or urokinase. There is usually radiologic evidence of catheter displacement.

The most effective method to deal with this complication is to perform a partial omentectomy. A laparectomy using a midline incision that does not involve the intramural catheter segment is performed. If omental trapping is confirmed excision of the intra-abdominal segment and partial omentotomy are done without disturbing tunnel or exit site. After wound closure, PD albeit with small volumes can be resumed without problems. Laparoscopic epiplopexy of the greater omentum has also been used in recent years to correct catheter malfunction by omental wrapping.

Catheter Migration

Catheter migration occurs less frequently following the advent of preshaved (permanently bent) catheters. Catheter migration is usually the result of improper implantation of silicone (thermoset) catheter as they try to regain their natural unstressed configuration. These are anecdotal reports of successful retrieval of migrated catheters using laparoscopy or guide wire manipulation under fluoroscopy [27, 34]. The only effective long-term solution of the problem is catheter replacement.

Access Efficiency and Dialysis Adequacy

As the adequacy issues of PD have become better understood it has become apparent that “access adequacy” is a critical factor in the dialysis adequacy equation. Access adequacy is determined by the interplay of the catheter design and specification and the degree of stability of the catheter, skin and environment interface (which is largely determined by the implantation method and subsequent care).

Properly implanted modern catheters have the potential to increase the success and efficiency of PD by consistently providing optimal dialysate flow without requiring special care or effort or interfering with patient comfort.

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Complications during Hemodialysis

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Introduction

Hemodialysis is the most successful and most commonly used form of organ replacement therapy. Its success and worldwide use attest to its safety. Advances in dialysis technology (both in machinery and disposable parts) contribute significantly to the safety of this therapeutic modality. Awareness of the potential complications of the procedure should facilitate preventive and remedial interventions. While many of the acute complications of hemodialysis are not immediately life threatening, they do add to the morbidity of dialysis patients and to the overall cost of the therapy.

Cardiovascular Complications

Hypotension

Clinical Features

Intradialytic hypotension (IDH) is one of the most common complications observed during hemodialysis. Cross-sectional studies suggest that it occurs in about a third of patients. Prospective longitudinal studies placed the incidence closer to 15% of all treatments [1]. Its occurrence is closely correlated with other symptoms such as cramps, nausea and vomiting. Predisposing factors appear to be a low body mass (women in particular), advanced age and the presence of cardiovascular disease [1]. The incidence of symptomatic hypotensive episodes is particularly high in patients who have normal or low blood pressure at the initiation of dialysis and in patients who have large interdialytic weight gains [2]. The development of IDH does not seem to be influenced by the type of hemodialysis membrane used [3].

Some authors have distinguished between two types of IDH based on the temporal behavior of blood pressure [4]. In one type (gradual hypotension), blood pressure declines gradually during hemodialysis with eventual appearance of symptoms. The other type is more acute (sudden hypotension) characterized by an abrupt and sharp fall in blood pressure along with the appearance of symptoms. While some mechanistic differences have been proposed to distinguish between the 2 types [4], it is unclear at present whether these types tend to occur in distinct subsets of patients and whether separate predisposing factors can be identified.

Pathophysiology

To understand the pathogenesis, etiology, and management of IDH, a brief review of the

determinants of arterial blood pressure on dialysis follows. Mean arterial pressure (MAP) is determined by peripheral vascular resistance (PVR) and cardiac output. Cardiac output is a function of stroke volume (SV) and heart rate, and SV in turns depends upon plasma volume (PV) and myocardial contractility. During ultrafiltration and/or dialysis, reduction of PV will result in hypotension if compensatory changes in myocardial contractility, heart rate, or PVR do not occur. During conventional dialysis, the reduction in plasma osmolality (P_{osm}) favors fluid shifts from the extracellular fluid compartment (ECF) to the intracellular fluid compartment (ICF), exacerbating the volume depleting effects of dialysis. The reduction in PV with both ultrafiltration and hemodialysis also leads to an increase in plasma oncotic pressure and a decrease in capillary hydrostatic pressure. Both of these forces mobilize fluid from extravascular spaces. The degree to which PV decreases thus depends not only on the rate of ultrafiltration and ICF shifts, but also on the plasma refilling rate from intracellular and interstitial fluid (ISF) compartments.

Volume-dependent Factors

While fluid removal during hemodialysis occurs from the intravascular space, refilling from interstitial fluid is effective enough that by the end of a typical dialysis treatment there is a greater reduction in interstitial fluid volume than in plasma volume. Vascular refilling depends on the rate and degree of ultrafiltration by hemodialysis as well as on other patient-related factors such as body size, fluid status, regional blood flow distribution, plasma osmolality and plasma protein concentration [5]. Refilling takes place during ultrafiltration and continues after cessation of fluid removal. Salt and water alterations (under condition of ultrafiltration with normal-sodium or high-sodium dialysate) are restricted mostly to the ECF component of the total body water [6]. In the ECF, it is principally the ISF that buffers salt and water depletion. The ISF is therefore, the buffer zone which maintains the proper balance and relationship between vascular capacity and volume. In end-stage renal disease (ESRD), interstitial colloid osmotic pressure is reduced and transcapillary colloid osmotic gradient is raised, conditions that would favor refilling [7]. After hemodialysis, interstitial colloid osmotic pressure tends to rise indicating fluid loss, but the transcapillary gradient remains in favor of refilling [7].

The dependence of refilling on interstitial hydration would imply that overhydration is associated with better refilling. Moreover, as ultrafiltration proceeds and the interstitial volume gradually contracts, one would expect a progressive drop in refilling rate over the course of a hemodialysis session. This formulation is consonant with the observation that IDH occurs usually during the latter half of a hemodialysis run.

Maneuvers that are aimed at enhancing vascular refilling would be expected to have a salutary effect on the occurrence of vascular instability during dialysis. Sodium modeling [6, 8, 9] has been shown to be effective in this regard. Improved hemodynamic stability utilizing sodium bicarbonate dialysis may be due, in part, to a greater plasma refilling and a better preservation of plasma volume. Underestimation of postdialytic dry weight will cause interstitial dehydration and consequently a low refill capacity. Maintenance of intravascular fill such as with red blood cell transfusions in anemic subjects reduces the short-term frequency of hypotensive episodes [10].

The latter half of dialysis does not always correspond to the maximal reduction in

plasma volume. In many patients, there is usually no sharp fall in blood volume nor any change in the plasma refilling rate at or before the time that IDH takes place [11]. This observation suggests that IDH is caused by a sudden breakdown of the blood pressure support mechanism compensating for a contracted blood volume.

Vascular Tone-related Factors

During hemofiltration and sequential ultrafiltration, the patient's ability for vasoconstrictive counterregulation is better maintained than during conventional hemodialysis [12]. Hemodynamic studies have repeatedly shown that while significant reduction of cardiac output, SV, pulmonary artery pressure and PV are observed during hemodialysis, only a minimal elevation in PVR is observed [12].

Inappropriate peripheral venodilatation has been proposed as an important contributor to the development of IDH [13 – 15]. Bradley et al. [14] found that while vascular resistance in the forearm rose during dialysis with acetate and with bicarbonate (more so with the latter), the venous bed of the forearm dilated. Maeda et al. [13] in a hemodynamic study found a sharp drop in cardiac output during IDH, along with concomitant sudden drops in the mean pulmonary arterial pressure and in the mean right atrial pressure. These changes have been attributed to a reduction in venous return [15]. Since there was no recognizable alteration in blood volume with the sharp fall in blood pressure, this curtailment in venous return is believed to be caused by a relocation of circulating blood, possibly associated with a sudden decrease in venous tone [13].

Converse et al. [16] likened the development of sudden hypotension during hemodialysis to that encountered in hemorrhage-induced hypovolemia. The latter can trigger a sudden fall in sympathetic activity resulting in bradycardia and vasodilatation. A similar type of vasodepressor reaction developing during dialysis would exacerbate the volume-dependent decline in blood pressure. Furthermore, Converse et al. compared the hemodynamic and sympathetic nerve activity (using intraneural microelectrodes for measurement) responses during hemodialysis in patients with and in those without a history of IDH. While progressive rises in vascular resistance and sympathetic activity were observed in the hypotension-resistant patients, in the hypotension-prone patients, however, the precipitous fall in blood pressure was accompanied by reductions in sympathetic activity, PVR, and heart rate as well as symptoms of vasodepressor syncope. These findings indicate that in some hemodialysis patients, hemodialysis-induced hypotension is not caused by a chronic uremic impairment in arterial or cardiopulmonary baroreflexes but rather by an acute, paradoxical withdrawal of sympathetic vasoconstrictor drive. Such a withdrawal often engenders a vasodepressor syncope [16].

Autonomic Neuropathy

Abnormalities of autonomic function have been observed in patients with chronic renal failure (CRF) both before and after initiation of maintenance dialytic therapy. The cold pressor test, response to sudden loud noise and mental arithmetic maneuvers were normal in non-dialyzed patients with CRF suggesting an intact efferent sympathetic pathway [17]. Expiration/inspiration ratio, lying/standing ratio, Valsalva ratio and the baroreceptor sensitivity slope were significantly abnormal in nondialyzed patients. These results indicate a defective parasympathetic pathway and a depressed baroreceptor sensitivity [17]. The heart rate response to

standing and the baroreceptor sensitivity are significantly lower in patients who develop IDH [17]. Similarly, Hebert et al. [18] found that day/night blood pressure variations were significantly reduced in patients with CRF when compared with a control population. Hemodialysis patients had a 'square wave' response to the Valsalva maneuver. In this group of patients, the IDH was not due to left ventricular dysfunction, but to a failure of the baroreceptor response to volume depletion during hemodialysis. Lilley et al. [19] have suggested that IDH may result from a lesion in the baroreceptors, cardiopulmonary receptors, or visceral afferent nerves.

Role of Dialysate

IDH is more common during acetate dialysis compared to bicarbonate dialysis, particularly in elderly subjects [20]. This phenomenon has been attributed to a slower metabolism of acetate as reflected in lower post-dialysis plasma bicarbonate concentrations [20]. Hyperacetatemia results in a decrease in preload, a finding compatible with the venodilatatory effect of acetate [21]. Indeed, Bradley et al. [14] have shown that the rate of fall of blood pressure was significantly greater during dialysis using acetate compared with that using bicarbonate. In addition, acetate dialysis led to a smaller rise in PVR and a greater venodilatation.

Prevention

A variety of therapeutic measures have been used to prevent and treat IDH (Table 1). Generally, ultrafiltration rates in excess of 0.3 mL/kg/min (1.2 L/hr in a 70 kg patient) should be avoided.

Patient Factors

As at least one type of dialysis hypotension is dependent on the volume of fluid removed, it is important that the patients should strive to gain as little weight as possible between dialysis treatments. It is doubtful that this limitation in weight gain can be accomplished with restrictions of fluid intake as almost all patients present with a normal pre-dialysis serum sodium value on the day of dialysis. The underlying mechanism, therefore, appears to be related to the development of thirst as a result of sodium intake. Consequently, in order to curtail weight gain, sodium intake must be restricted. Patient education is a very time-consuming process and the return on inadequate effort is often regrettably meager. Most dialysis patients gain about 1 kg of weight daily. This must mean that the patient's sodium intake is close to 9 g of sodium chloride (154 mmol), a value approximating a normal intake in most of the developed world. Nevertheless, limiting sodium intake is the key to a successful treatment. The limitation on weight gain, however, should not lead to reduction in food intake or compromise adequate nutrition. Meticulous blood sugar control in diabetics is mandatory to avoid excessive thirst. Some patients have abnormal thirst and present with hyponatremia. Angiotensin converting enzyme (ACE) inhibitors are useful antidipsogenic agents. Patients should also be told not to eat shortly before dialysis if they are prone to hypotension to avoid the contribution of postprandial blood pressure drop [22]. It is also prudent to withhold short-acting blood pressure medications shortly before dialysis.

Dialysis Procedure

A longer dialysis session which curbs the amount of ultrafiltration per time unit may be beneficial. The use of linear or modeled ul-

Table 1. Strategies for Prevention and Management of Intradialytic Hypotension

I. Prevention

1. Patient Factors
   - Avoid excessive interdialytic weight gain (< 5% of body weight)
   - Frequent assessment of dry weight
   - Low sodium diet
   - Meticulous diabetes control
   - Avoid antihypertensive drugs prior to dialysis
   - No food on, or just prior to, dialysis
   - Reduce intake of narcotic analgesics and sedative hypnotics
   - Improve nutritional status and hypoalbuminemia if present
   - Increase hematocrit to ≥ 33% (target 33 – 36%)
   - Evaluate for silent pericardial effusion
   - Administer prophylactic oxygen, especially in elderly with cardiac and/or respiratory disease and predialysis P_aO_2 < 80 mmHg
   - Ameliorate risk factors for LVH

2. Dialysis Procedure
   - Avoid ultrafiltration rates > 1.2 L/hr (0.3 mL/kg/minute) [slower, longer dialysis]
   - Use dialysis machines with ultrafiltration controls
   - High dialysate sodium (140 – 145 mEq/L)
   - Sodium ramping programs
   - Bicarbonate dialysis (especially with high blood flow)
   - Higher dialysate calcium (3.5 mEq/L)
   - Lower dialysate temperature (34 – 35°C)
   - Sequential ultrafiltration/dialysis (occasionally necessary when high UF rates are required)

3. Pharmacologic
   - Hyperoncotic albumin (20 – 25%)
   - Midodrine (ProAmitine)
     - 2.5 – 5.0 mg 30 – 45 minutes prior to dialysis. Alternately, 2.5 md bid on dialysis days, 1.25 mg bid on non-dialysis days
   - Others: mannitol, L-DOPA, L-carnitine

II. Acute Treatment

Volume	[200 mL boluses of isotonic saline, hypertonic saline (10 mL 23%), Mannitol (50 mL 20%), Dextran 70 (100 – 500 mL 6%)]
Vasoconstrictors:	Phenylephrine, metaramine, norepinephrine, midodrine, dopamine

trafiltration using volume controllers may be of help; so may sodium modeling (Figure 1) with a higher sodium dialysate level during the early part of dialysis [23]. Sequencing dialysis with separation of ultrafiltration and hemodialysis is not uniformly successful and the logistic burden may preclude its applicability.

Dialysate Cooling

The greater cardiovascular stability encountered during isolated ultrafiltration has been related to the cooling of blood in the extracorporeal circuit by as much as 2° C [24, 25]. This observation lends support to the suggestion that lowering blood temperature

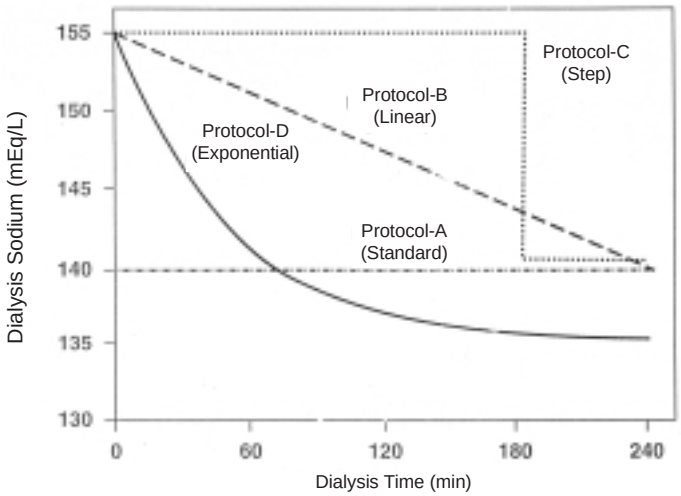

Figure 1. Graphic presentation of the 4 dialysate sodium delivery protocols: Protocol A, standard dialysis (sodium of 140 mEq/L); Protocol B, linear ramping (initial dialysate sodium of 155 mEq/L, continuous decline to 140 mEq/L by the end of dialysis); Protocol C, stepwise ramping (dialysate sodium of 155 mEq/L for the first 3 hours and 140 mEq/L for the last hour of dialysis); and Protocol D, exponential program (a smooth curve reduction of dialysate sodium from the entered percent maximum of 155 mEq/L to 135 mEq/L baseline level 2 hours before the end of dialysis). Program D result in a geometric mean dialysate sodium of 143 mEq/L, a value higher than the 140 mEq/L of standard dialysis.

during hemodialysis may afford a similar advantage [24]. Lowering dialysate temperature from 37° to 35°C significantly reduces the incidence of IDH [24, 25]. While the decline in incidence has been reported to be dramatic in short-term studies [24], the overall reduction in incidence in prospective long-term studies has been modest [25, 26]. Moreover, the possibility of having a placebo effect has also been raised [25]. Greater elevations in PVR and higher post-dialysis catecholamine levels suggest that dialysate cooling may enhance vasoconstrictor mechanisms. In one study, dialysate cooling brought about a greater incidence of cramps [26].

Modulated Dialysis

Determination of blood volume changes by continuous monitoring has allowed the development of blood volume controlled ultrafiltration. Such measures have resulted in a lower incidence of symptomatic IDH [27].

Membrane Type and PD

Large studies have found no effect of membrane type on blood pressure values during dialysis [3, 28, 29]. Should a patient have excessive hypotension, dialytic therapy should be switched to PD.

Pharmacological Manipulation

Hyperoncotic albumin 20 – 25% may prevent hypotension and allow more ultrafiltration to take place. If given, albumin should be infused rapidly during the first 15 – 30 minutes of dialysis to promote mobilization of any edematous fluid that may be present. The excessive fluid can then be removed by ul-

trafiltration. Nasal oxygen has also enabled some patients to maintain blood pressure; so have mannitol infusions. These infusions, however, cannot be given for more than 3 or 4 dialyses because of the problem of accumulation.

Miscellaneous Treatment

Elevating the legs or using compressive bandages may facilitate mobilization of the edema and allow more ultrafiltration to proceed with less blood pressure problems. Similarly, raising the hematocrit (HCT) by transfusions or by erythropoietin (rHu-EPO) therapy has curtailed the incidence of IDH in some patients. It is also important to provide patients with appropriate stimulation since simply the boredom of lying and waiting may worsen hypotensive episodes.

Acute Treatment

Volume Administration

The management of IDH has relied on volume expansion irrespective of the underlying mechanism in each particular patient. Volume expansion has frequently been done by infusions of normal saline, a practice that frustrates attempts to attain dry weight by increasing the fluid burden, thus necessitating greater ultrafiltration and further hypotension. As a consequence, a vicious cycle is created. The volume overload present in between dialysis sessions gives rise to hypertension that necessitates the use of antihypertensive agents. Such use aggravates the hypotension occurring during dialysis.

Hypertonic saline solutions safely and effectively treat IDH and may offer a better alternative. When a patient is given equal osmolal loads, the more concentrated solutions produced a greater increase in systolic blood pressure. The addition of an oncotic agent such as dextran may prolong the blood pressure response [30].

Dextrans are useful plasma expanders to employ in the management of hypotension. Recent autopsy and biopsy reports [31], however, have documented the intracellular deposition of dextrans in various tissues such as lymph nodes, the heart, adrenals, the bone marrow and others. A similar problem may be encountered with mannitol as the fate of this non-metabolizable alcohol is also unknown.

Vasoconstrictors

As at least some of the pathophysiology of dialysis hypotension appears to be due to vasodilatation, simply giving the patient vasoconstrictors such as metaramine, phenylepinephrine, norepinephrine, midodrine, amezinium, vasopressin or caffeine, has been associated with better maintenance of blood pressure [32, 33].

Midodrine, a selective peripherally-acting α-receptor agonist, has been studied extensively in the treatment of neurogenic orthostatic hypotension. It elevates blood pressure by both a constrictor effect on the arterioles and venous capacitance vessels as well as through an increase in cardiac output based on a decrease in venous pooling and augmented venous return. It has minimal cardiac and central nervous system (CNS) effects, by virtue of its α1-receptor specificity and its inability to cross the blood brain barrier.

Experience with midodrine in dialysis patient is limited and only 3 studies in patients with ESRD have been published [33 – 35]. In the small number of patients studied, midodrine therapy improved blood pressure stability and clinical symptomatology. Since the active metabolite (deglymidodrine) of midodrine is renally excreted, the dose should be

reduced in dialysis patients. A dose of 2.5 – 5.0 mg administered 30 – 45 minutes prior to dialysis, seems effective. Doses of 2.5 mg twice daily on dialysis days and 1.25 mg twice daily on non-dialysis days were also found effective.The most serious adverse reaction is supine hypertension, which has been reported in 8% of patients in one study, and may require discontinuation of therapy.

Arrhythmias

Arrhythmias are frequent occurrences in patients on hemodialysis with reported incidences varying from 30 – 48% of patients [36, 37]. These abnormalities can span from supraventricular to severe ventricular arrhythmias. There is an increased frequency of occurrence clustering around dialysis time [36, 38]. Identified predisposing factors include increased left ventricular mass, advanced age, pre-existing ischemic heart disease, potassium depletion, and the duration of ESRD. IDH, which may impair coronary perfusion, acute shifts in electrolytes (particularly potassium) conduction system calcifications, and digitalis therapy are other predisposing risk factors.

Left ventricular mass is increased in the majority of dialysis patients, both normotensive and hypertensive [37], and, as in patients with normal renal function, represents a major risk factor for ventricular arrhythmias. The wide electrolytic and volume changes taking place during dialysis may create a window of vulnerability leading to serious arrhythmic consequences. The presence of pericarditis is also associated with a heightened frequency of supraventricular arrhythmias [39]. The elevation of plasma calcium concentration during hemodialysis might induce either reentry-activity or triggered-activity types of arrhythmias during treatment. Use of dialysate with a lower calcium concentration reduces the incidence of arrhythmias in certain subjects [40].

A higher frequency of ventricular arrhythmias was encountered during acetate dialysis than during bicarbonate dialysis [38]. The quicker and more regular correction of acidosis with bicarbonate dialysis and the consequent difference in ionic flows between the intra-and extracellular spaces, could account for the seemingly less arrhythmogenic effect of bicarbonate dialysis [38].

Treatment of arrhythmias during hemodialysis is much the same as in non-dialysis situations except that in ESRD the altered pharmacokinetics and protein binding of drugs should be taken into account.

Hypertensive Emergencies

Sometimes during dialysis and ultrafiltration a paradoxical hypertensive response occurs. This hypertensive response to hemodialysis may be due to exaggerated vasoconstrictor responses to fluid removal. In some patients, we have observed a dramatic rise in plasma catecholamines in parallel with the increment in blood pressure, and an abrogation of the hypertensive response with phentolamine administration. Alternatively, activation of the renin-angiotensin system as a result of volume depletion may be contributory. However, since the paradoxical hypertension has been observed both in the absence of changes in sympathetic activity and in anephric subjects, the above mechanisms cannot be claimed to occur uniformly in all subjects with the condition. The occurrence of this hypertensive response to fluid removal does not appear to be related to the dialysate calcium level. Hypertensive patients are usually instructed to withhold their antihyperten-

sive medications on the day of dialysis to avoid IDH. The persistent elevation of blood pressure at the end of dialysis may represent a rebound of antihypertensive withdrawal which should respond promptly to resumption of medications. Under conditions when the physician considers that such delays may be injurious to the patient, immediate therapy is in order. The real need for institution of urgent antihypertensive therapy has to be clearly established particularly as a delayed hypotensive response to hemodialysis may be observed. The simple resumption of the patient's established antihypertensive regiment may be sufficient in the majority of cases.

Pericarditis with Pericardial Effusion

Pericarditis in ESRD patients can be categorized into 2 varieties, namely, uremic pericarditis and dialysis pericarditis [41]. Uremic pericarditis, a manifestation of renal failure, occurs in individuals who have never received dialytic therapy and often responds to intensive dialysis, e.g. daily 4-hour dialysis runs for 2 – 3 weeks. Dialysis pericarditis, on the other hand, occurs in patients who have already been treated with maintenance dialysis for a period of time. Although most authorities believe that dialysis pericarditis is a manifestation of inadequate dialytic therapy, this form of pericarditis may not readily respond to intensive dialysis (only about 40% of patients respond [45]). Because of this peculiar characteristic, it has been suggested that this form of pericarditis might be of viral origin [42].

Patients with pericarditis often present with precordial pain, hypotension, dyspnea, fever and rapid weight gain due to fluid overload. A pericardial friction rub may be heard. A large percentage of pericarditis patients may develop pericardial effusion. Patients with significant pericardial effusion tend to be intolerant of fluid removal by ultrafiltration, presumably because a high venous pressure is required to maintain adequate cardiac filling and cardiac output. When this high venous pressure is lowered by fluid removal during ultrafiltration, reductions in venous return, cardiac output and blood pressure are the consequences. Should fluid removal by ultrafiltration be excessive for the degree of pericardial effusion, cardiac tamponade characterized by tachycardia, hypotension and a rising venous pressure may result. Death from cardiac tamponade is not uncommon. Noteworthy is the fact that in many patients suffering from cardiac tamponade, a pulsus paradoxus may not be demonstrable [43].

Since patients with pericardial effusion are prone to develop hypotension during ultrafiltration, large volumes of saline are frequently administered intravenously to combat this untoward effect. As a consequence, an already substantial state of overhydration is often aggravated.

It should be noted that the amount of fluid necessary to produce tamponade may be as little as 250 mL when the fluid accumulates quickly, or over 2 L in slowly developing effusions when the pericardial sac has had the opportunity to stretch and adapt to the increasing volume of fluid. In addition, a pericardial effusion accumulating in a previously healthy distensible pericardial sac has less hemodynamic effect than that of an effusion developing in a previously diseased, non-compliant pericardial sac. Finally, certain dialysis patients have a small amount of fluid in their pericardial sacs. These small effusions have no clinical significance [44].

Diagnosis of pericardial effusion is based on a high index of suspicion and best confirmed by echocardiography. Once the diagnosis is established, further dialysis should be

performed with a heparin-free technique to minimize the risk of developing hemopericardium. Intensive dialysis should be carried out daily for 2 – 3 weeks, using a higher dialysate potassium value than normal (e.g. 3.5mmol or so instead of 2mmol if removal of potassium by the daily dialysis is excessive), and a lower dialysate buffer base level than usual (if metabolic alkalosis develop). Should dialysis-induced hypophosphatemia appear likely, dialysate can be enriched prophylactically with phosphate salts.

In order to avoid the risks associated with intensive dialysis, and since dialysis pericarditis with effusion responds less readily to intensive dialysis, prompt surgical drainage of moderately large (e.g. 250 mL) or very large effusions has been recommended [45]. With regard to surgical drainage, we prefer the subxiphoid pericardiotomy approach utilizing local anesthesia and a large-bore drainage tube with or without the topical instillation of non-absorbable steroids [46]. Should local drainage fail, pericardiectomy or pericardial fenestration is usually required.

Pulmonary Complications

Hypoxemia

Clinical Features

Patients maintained on intermittent hemodialysis harbor a continuously changing acid-base internal environment. In the interdialytic period, the progressive accumulation of non-volatile acids leads to a compensatory hyperventilation. During dialysis, retitration of the retained acids takes place along with a gain of alkali and an abatement of the hyperventilation, only to have the acidosis recur as the acid burden progressively rises postdialysis [47]. The intradialytic period is more complex and involves changes in both oxygen and carbon dioxide levels.

Hypoxemia of variable degrees and duration occurs in the intradialytic period. In some subjects it occurs early and is of short duration, while in others it may have a late onset and be prolonged [48]. The latter pattern has been associated with a heightened release of tissue plasminogen activator (TPA) [48]. The hypoxemia is especially pronounced in patients with preexisting pulmonary abnormalities in that it may persist postdialysis. Continuous measurements of oxygen saturation reveal a drop in saturation of 1 – 4% coinciding with the observed hypoxemia [49]. The hypoxemia is usually innocuous except when severe in patients with underlying respiratory decompensation, or in subjects with partially compensated ischemic heart disease who may experience anginal episodes necessitating oxygen supplementation for prevention. There is no relationship between dialysis-induced hypoxemia and hypotension [50].

Pathophysiology

Effects of Dialysate

Most studies agree that acetate dialysis is associated with a more severe hypoxemia than bicarbonate dialysis or isolated ultrafiltration [47]. The role of dialysate composition in the genesis of hypoxemia has been elegantly illustrated by the study of Francos et al. [51]. Patients were studied with both polyacrylonitrile (PAN) and cuprophan membranes containing different priming solutions. Despite leukopenia and complement activation, hy-

poxemia did not occur during membrane contact only. After 15 minutes of subsequent acetate dialysis, significant hypoxemia occurred with both membranes. Significantly less hypoxemia was noted during bicarbonate dialysis.

While there is general agreement that carbon dioxide unloading is a primary factor in the genesis of the hypoventilation and the associated hypoxemia, the mechanisms of carbon dioxide unloading remain a subject of debate. During acetate dialysis, a significant loss of carbon dioxide and bicarbonate takes place across the dialyzer. The resultant hypocapnia has been assumed to give rise to hypoventilation and subsequent hypoxemia [52]. Another possible cause for the hypocapnia has been advanced by Oh et al. [53]. These authors suggested that the loss of carbon dioxide was too small to alter significantly carbon dioxide balance and that greater carbon dioxide consumption occurs with metabolism of the acetate acquired during dialysis.

Hypoxemia has also been observed with bicarbonate dialysis, albeit of a much milder degree. In this setting, hypoxemia has been related to the degree of alkalization induced by a high-bicarbonate bath [54]. By raising the affinity of hemoglobin for oxygen, such alkalization would reduce tissue oxygen delivery and thereby magnify the clinical effects of dialysis-induced hypoxemia [55].

Effect of Membrane

If pulmonary leukosequestration plays a role in dialysis-induced hypoxemia, then membranes with differing complement-activating potentials and varying ability to induce neutropenia would be expected to cause disparate degrees of hypoxemia in proportion to their neutropenic effects. Under conditions of acetate dialysis, however, no differences in the degree of hypoxemia have been observed between membranes [52, 56, 57]. These observations may be explained by the different time course of pulmonary leukosequestration and hypoxemia. Ross et al. [58], using indium-radiolabelled leukocytes, found similar degrees of pulmonary leuko sequestration with both acetate and bicarbonate dialyses. However, hypoxemia developed later in the course of dialysis and was seen only with acetate dialysis.

Taken together, these observations suggest that the main mechanism of dialysis-induced hypoxemia is carbon dioxide unloading with minor contributions from other mechanisms, and that difference between membranes are not clinically significant.

Musculoskeletal and Skin Complications

Muscle Cramps

Clinical Profile

Muscle cramps represent a vexing and persistent problem plaguing a significant number of patients maintained on hemodialysis. Such cramps develop repeatedly in about 25% of all hemodialysis patients [59]. While benign in its biological significance, the clinical and emotional toll of the condition can frustrate the most stoic of patients. Painful cramps, usually of the lower extremities, occur in the second half of a dialysis session and are sometimes preceded by hypotension. A delayed course is also observed and cramps can recur over several hours after the end of a dialysis run. Cramps are commonly observed in the setting of rapid ultrafiltration (even if all the

excess fluid has not yet been completely removed), or when a patient's volume status falls below the empirically determined dry weight.

Pathophysiology

There have been very few studies examining the mechanisms underlying the appearance of muscular cramps during or after hemodialysis. Since cramps take place in a setting of relative hypovolemia developing as a result of the discrepancy between the magnitude of the ultrafiltration and the vascular refilling rate, a role for volume contraction in their genesis has been entertained. This assertion is supported by the common observation that volume expansion with hypertonic solutions frequently brings relief. Electromyographic measurements in cramp-prone subjects during dialysis demonstrated a progressive rise in tonic activity during the second half of hemodialysis culminating in the paroxysm of the cramp [60].

Vasoconstrictor mechanisms activated by volume removal are plausible mediators of reduced muscle blood flow. The success of nifedipine in alleviating established cramps may be considered adjunctive evidence for a role of vasoconstrictor mechanisms [60]. Cramps, however, can continue to take place in hemodialysis patients treated with chronic calcium-channel blocker therapy. Piergies et al. [61] have shown that activation of the renin-angiotensin system has no role in the causation of skeletal muscle cramps during hemodialysis. The activation of the renin-angiotensin system was not unusually enhanced in patients with frequent cramps, nor did ACE inhibition reduce the frequency or severity of the cramps. In a follow-up study, the same investigators suggested that cramps were prone to develop during hemodialysis in patients whose sympathetic nervous system response to volume stress was partially intact since a greater ratio of tilt/recumbent norepinephrine levels was demonstrated in patients with frequent cramps than in those who cramped infrequently [62]. The role for a more marked sympathetic nervous system response to volume stress in patients who have cramps is supported by the observation that small doses of prazosin given at the beginning of a dialysis session significantly reduce the frequency of cramps when compared to administering a placebo [63]. The use of prazosin, however, was associated with an increase in the incidence of hypotension making the intervention not clinically useful.

Tissue hypoxia has been suggested as a cause for dialysis-induced cramps. Cramping, however, is not usually a feature of extremity ischemia and the relief of the pain with maneuvers that do not alter oxygen delivery, makes this hypothesis less likely. The observation that L-carnitine supplementation is associated with a reduced incidence of muscle cramps has led to the formulation of the hypothesis that uremic cramps may be due to carnitine deficiency [64]. The latter, however, causes myopathy rather than cramps, and when carnitine deficiency-related cramps develop, they usually take place during exercise and not at rest. It is clear from the above that while many of the conditions associated with cramps are known, a definitive pathophysiologic scheme relating cramping to one or several of such conditions, is at present lacking.

Management

Hypertonic Solutions

Hypertonic solutions of dextrose, mannitol, and saline are effective treatments for hemo-

dialysis-associated muscle cramps. The concern that post-dialysis retention of mannitol and saline may lead to increased thirst, interdialytic weight pain, and elevated blood pressure has not been validated. In a prospective, randomized, double blind crossover study the safety and efficacy of the three solutions have been found to be equivalent [65]. Cramps can be treated with 50 mL (126 mOsm) 50% dextrose water, 100 mL (138 mOsm) 25% mannitol, and 10 – 15 mL (126 mOsm) 23.5% saline. Saline solutions of lower concentrations can also be used. Mild postdialysis hyperglycemia and hypernatremia during administration of dextrose and saline, respectively, are the only significant laboratory abnormalities observed [65].

Drug Therapy

Both quinine (325 mg orally at bedtime) and vitamin E (400 IU orally at bedtime) are effective in reducing the incidence and severity of leg cramps in hemodialysis patients. The effect of these drugs is observed early (within 2 weeks of therapy) and has been found to be maintained in short-term studies (up to 2 months) [66]. The two drugs have similar efficacy, but it is not known whether their effects are additive or whether subjects unresponsive to one agent would respond to the other. Quinine reduces the excitability of the motor endplate to nerve stimulation and enhances the muscle refractory period. The drug is cleared primarily by the liver and toxicities, while serious, are very rare with the usually prescribed dosages [60]. Variability in response among patients may be related to the drug's variable bioavailability. There is anecdotal evidence that administration of chloroquine phosphate (a drug effective in alleviating ordinary cramps) may reduce the frequency of cramps during hemodialysis [67], the side effects of the drug need to be considered before chronic use.

L-Carnitine Supplementation

Several studies have suggested that correction of the carnitine deficiency of uremia may have a salutary effect on the musculoskeletal symptoms associated with hemodialysis. A double-blind, placebo-controlled, and randomized study in a large sample of long-term hemodialysis patients, showed a decrease in the incidence in intradialytic cramps with L-carnitine supplementation given intravenously at the end of a dialysis session. This improvement was observed in association with a reduction in the incidence in intradialytic hypotension, which frequently accompanies cramping, and improvement in muscle mass and several biochemical parameters [64].

Modulated Dialysis

The frequent association of hypotensive episode and the development of cramps has encouraged the examination of the effects of maneuvers aimed at alleviating hypotension on the incidence of cramps. Sodium modeling and blood volume-controlled ultrafiltration have reduced the incidence of hypotension and cramps in parallel [27].

Acute Allergic Reactions

Clinical Features

Allergic reactions occurring immediately after the initiation of dialysis using new dialyzers (also known as the 'first-use syndrome') consist of a constellation of many of the following symptoms: burning retrosternal

pain, burning sensation along the arteriovenous fistula, sensation of diffuse heat, cold perspiration, urticaria, pruritus, periorbital and facial edema, flushing, laryngeal stridor, bronchial hypersecretion, bronchospasm, dyspnea, hypotension, bradycardia, and loss of consciousness. Death can occur [68].

Pathophysiology

Sterilant-related

Acute allergic reactions occurring when new dialyzers were used, were claimed to be due to cuprophan, but subsequently were linked to the sterilant ethylene oxide. Such reactions were more common with the use of hollow-fiber dialyzers than with the use of parallel plate and coil dialyzers [69].

Ethylene oxide (ETO) has been clearly implicated in the causation of a majority of cases of acute anaphylactic reactions to new dialyzers [70, 71]. The higher incidence of the first-use syndrome in the case of hollow-fiber dialyzers is believed to be related to the universal presence of the polyurethane potting material which functions as a reservoir for ETO. Removal of ETO from dialyzers is directly related to the volume of rinse, the temperature of the rinsing solution, and the duration of storage of the dialyzers prior to use. Priming solutions that have remained within the blood compartment of a dialyzer for a substantial length of time should be discarded and not be given to the patient. This is because ETO can diffuse from the potting material into the priming solution to reach an inordinately high level.

Specific ETO-related IgE antibodies are found in patients with hypersensitivity reactions to the sterilant [70, 71, 73, 74]. IgG antibodies, in contrast, are demonstrated in many hemodialysis patients who have never suffered from any hypersensitivity reactions. The presence of these antibodies denotes mere exposure [72]. Both cutaneous testing and enzyme-linked immunosorbent assay (ELISA) testing for assessing reactivity to ETO-human serum albumin can be carried out in hemodialysis patients with anaphylactic reactions. Cutaneous testing, while clinically simpler, offers no real advantage as the sensitivity, specificity, and negative predictive values of the 2 methods are similar [74].

In the majority of patients with anaphylaxis to dialysis, ETO has been identified as the etiologic agent. However, in a significant minority of patients sustaining such reactions, the responsible agent remains unidentified. Complement activation has been proposed as a mechanisms in some of the subjects with no identifiable antigen(s). No correlations between the time of onset of symptoms (if any symptoms were present) and the degree of complement activation were detected, however, among patients suffering from severe, moderate, or no hypersensitivity reactions [71], suggesting that complement activation plays no role in these reactions. Moreover, as mentioned above, hollow-fiber, parallel-plate and coil dialyzers of comparable surface areas activate complement to a similar extent [75]. If the complement activation were responsible for the dialyzer reactions, why should only hollow-fiber dialyzers be associated with a high incidence of the ‘first-use syndrome’? Anaphylaxis to formaldehyde during reuse has been reported [76]. In a few unique cases, allergic reactions continued to occur irrespective of modifications in dialyzer choice, in sterilization methods and in prophylactic measures [77]. Symptoms reminiscent of the first-use reactions have also been encountered during reuse. However, it has been suggested that the development of such reactions is not related to the type of disinfectant product the

reprocessing method (manual or automated), or the type of dialysate (bicarbonate, acetate, or both) [78]. Finally, anaphylactoid reactions have also been reported in patients who were dialyzed with reused dialyzers and receiving ACE inhibitors at the same time [79].

Membrane-related

Recently, however, acute allergic reactions have been reported when AN69 (a type of polyacrylonitrile membrane) dialyzers were used in patients taking ACE inhibitors [80, 81]. There is convincing evidence that this reaction is related to an early and vigorous production of bradykinin induced by the contact of blood (via the contact pathway) with the negatively-charged AN69 membrane. In the setting of using the AN69 membrane along with an ACE inhibitor, bradykinin accumulates in the blood because ACE inhibitors block the action of the enzyme kininase II which is responsible for the destruction of bradykinin.

Pruritus

Clinical Features

The incidence of pruritus is high in dialysis patients. At present, at least 50% of patients maintained on dialysis suffer from itching [82, 85]. The prevalence of pruritus seems to rise with the duration of dialysis. This finding has led to the postulate that either the dialytic procedure contributes to the development of itching, or, the longer survival made possible by dialysis and the failure of dialysis to correct the uremic state fully, combine to allow pruritogenic mechanisms to become more manifest.

Continuous monitoring studies [83] in hemodialysis patients suffering from pruritus reveal that itching peaks at night, occurs relatively more often during dialysis treatment and the least often on the day following dialysis. These observations are consistent with the notion that the condition is improved by dialysis, suggesting that the accumulation of pruritogenic substances is of major importance in the pathogenesis of uremic pruritus. Contrary to this postulate, there have been reports [84] of pruritus occurring mostly during or soon after hemodialysis in some 25% of patients, and becoming more severe during dialysis in an additional 40% of subjects. This disparity in clinical behavior highlights an underlying heterogeneity in the clinical manifestations and in the pathophysiology of the disorder.

Pathophysiology

Although subjected to intense study, the mechanism(s) underlying pruritus in subjects treated with renal replacement therapy continues to elude a unifying formulation. Several mechanisms have been proposed that may be responsible, singly or in combination, for the development of this condition. It is clear, however, from the variance in the literature that a great deal of individual variations may be present and that a search for major contributory factors should be individualized. While uremic subjects are not immune to the myriad of conditions that induce pruritus in the general population, the following discussion is restricted to the pathophysiology of the itching that is peculiar to the uremic state.

Dryness or xerosis has been investigated as a possible cause of uremic pruritus. In xerosis, the stratum corneum epidermidis becomes devoid of water. Being very dry, the most super-

ficial layer functions like a foreign body. Scratching removes this superficial layer and relieves itching. Evidence for and against this mechanism has been advanced [82].

The observation that severe pruritus disappeared 2 – 7 days after subtotal parathyroidectomy in maintenance hemodialysis patients, suggested that either parathyroid hormone (PTH) or derangements in calcium or phosphate metabolism may be responsible for the pruritus [85]. Several lines of evidence favor a role for PTH in the genesis of pruritus in uremia. Patients with pruritus have significantly higher serum concentrations of PTH than those without [83]. Moreover, reduction of PTH values by control of hyperphosphatemia or by charcoal hemoperfusion brings about a reduction in pruritus. It is noteworthy that not all uremic patients with secondary hyperparathyroidism, even when severe enough to warrant subtotal parathyroidectomy, suffer from pruritus. These observations have led to the contention that additional factors may be operative in uremic pruritus.

Histamine has been implicated to play a major role in the pathogenesis of uremic pruritus. Plasma histamine values are higher in patients with CRF compared to those in controls [86]. Since histamine and its metabolites are normally excreted in the urine, the higher concentrations of histamine may be a consequence of its retention in renal failure. Furthermore, plasma histamine values were, in a few studies, shown to be significantly higher in hemodialysis patients with pruritus than in those without [86].

As mast cells and monocytes are known to be the main source of histamine production, several studies have investigated the relationship of these cells to pruritus in uremia. In some studies, the number of mast cells was found to be raised in patients undergoing maintenance hemodialysis [87]; and, in addition, patients with pruritus were discovered to have, in their skin, many, diffusely scattered and degranulated mast cells. Consequently the high plasma level of histamine might be a result of degranulation of the mast cells and the basophils. In contrast, Mettang et al. [88] found no relationship between the level of plasma histamine, the number of skin mast cells and the extent of pruritus in uremic patients. Moreover, Cohen et al. [89] showed that the number of mast cells was the same in itching dialysis patients and in controls who happened to be living-related kidney donors. Francos et al. [90] demonstrated that ketotifen, a mast cell stabilizer, was effective in reducing itching without causing any significant change in histamine level, histaminase activity or skin histamine content. Such an observation suggests that mast cell activation, separate from histamine release, may contribute to the pruritus in uremia. It is clear from this survey of possible etiologies that a unitary etiology or mechanism for the pruritus of uremia is not discernible. It is very likely that different factors may be operative in different subjects and while some common elements may be evident, individualization of evaluation needs to be observed.

Management

Since pruritus appears to be multifactorial in its pathogenesis, several modalities of treatment have been suggested. In some patients, dialysis is enough to relieve the itching; in others, however, pruritus starts during dialysis or is even exacerbated by dialysis. Some have suggested that pruritus may be alleviated by an improvement in the dialysis prescription as judged by urea kinetic modeling. Subtotal parathyroidectomy has been found to be successful in patients with secondary hyperpa-

rathyroidism who suffered from pruritus. However, this treatment is not effective in all cases, and not all uremic patients with secondary hyperparathyroidism suffer from pruritus either.

Sun exposure is known to relieve the pruritus associated with several unrelated dermatoses and sunburn doses of ultraviolet light from artificial sources are effective in treating uremic pruritus. In an extensive literature search focusing on the most effective treatment for uremic pruritus, Tan et al. [91] found that ultraviolet B (UVB) phototherapy is the treatment of choice in moderate to severe uremic pruritus. The response occurs more rapidly in patients treated 2 – 3 times weekly than in those treated once weekly. Recurrences can come about, but usually respond to new UVB treatments. Being rare and mild, side effects mainly consist of localized sunburn. The mechanism of action of UVB is unclear. Since many patients with generalized pruritus respond to half body phototherapy, it has been suggested that UVB can inactivate a circulating pruritogenic substance or induce the formation of an antipruritic substance that relieves the pruritus. UVB irradiation might inhibit mast cell granule release or might relieve pruritus by damaging the cutaneous nerves.

Several drugs have been used in the treatment of uremic pruritus, but all have met with varying degrees of success and of failure. Topical emollients are hydrophilic compounds that hydrate the skin and form an occlusive film that reduces evaporation. These medications are helpful in alleviating pruritus caused by dryness of the stratum corneum epidermidis. Although histamine is a major itch mediator, use of antihistamines is not consistently successful.

It is likely that pruritus will continue to plague patients and their physicians, and unless more definitive and practical therapeutic regimens are discovered, the management of this condition will remain problematic.

Hemolysis

A mild degree of hemolysis manifested by the presence of detectable free hemoglobin in blood is commonly observed during dialysis. This finding, however, is of minimal clinical significance and can be attributed to a variety of factors including mechanical trauma to the red blood cells and possibly complement activation [92]. Inherent changes in the red blood cells of uremic subjects which are thought to contribute to the mild chronic hemolysis observed in uremia, may predispose to this hemolysis. These inherent changes include increased red blood cell rigidity and fragility, and reduced deformability secondary to oxidative damage [93].

Clinically significant hemolysis is observed with technical problems related to the dialysis procedure itself. Kinked blood lines, contamination of dialysis fluid with hydrogen peroxide because of inadequate rinsing of the water treatment system after disinfection, residual formaldehyde in reused dialyzers, and accidental hypochlorite infusion, have all been reported to be associated with serious life-threatening hemolysis. Clinically, the affected patients complain of malaise, nausea, headache and severe abdominal pain. Death due to hyperkalemia may also occur.

Bleeding during Dialysis

The bleeding tendency of uremia is considered to represent an acquired defect in primary hemostasis. The most common clinical mani-

festations of uremic bleeding are the least severe, and include ecchymoses, purpura, epistaxis, gingival bleeding, and bleeding from venipuncture sites. Major hemorrhages, from gastrointestinal, retroperitoneal, pericardial, or intracranial sites, seldom develop spontaneously and frequently reflect underlying pathology.

Pathophysiology

A multiplicity of defects may underlie this bleeding diathesis. A precise pathogenetic framework continues to be elusive. While defects in blood coagulation factors, alterations of the fibrinolytic system, and vascular abnormalities have been considered to be contributory, platelet dysfunction has been the most consistently described hemostatic abnormality in patients with ESRD [94]. Uremic platelets exhibit reduced adhesion to vascular subendothelium and impaired aggregation response to various stimuli such as ADP, epinephrine, collagen, and thrombin. Abnormal platelet aggregation improves after hemodialysis. Altered interaction of adhesive macromolecules such as fibrinogen and von Willebrand factor (vWf), with platelet membrane glycoproteins have been suggested to contribute to the aggregation and adhesion defects.

Uremia results in a defect in platelet adhesion to subendothelial structures, thus contributing to the increased bleeding tendency. Fibrinogen receptor function of platelets from chronic renal failure patients is impaired. Hemodialysis improves fibrinogen binding indicating removal of a uremic inhibitor by dialysis treatment. The defect is reproduced in normal platelets when they are incubated in predialysis uremic plasma, but not with postdialysis plasma. CRF patients treated with recombinant human erythropoietin (rHu-EPO) for correction of anemia show amelioration of platelet dysfunction [94].

Management

Treatment of uremic platelet dysfunction and uremic bleeding is summarized in Table 2.

Dialysis

Both peritoneal dialysis and hemodialysis can lead to correction, often only partial, of the uremic hemostatic defect. Moreover, adequacy of dialysis has been suggested to be an important factor in the improvement in bleeding tendency. Platelet fibrinogen receptor function is ameliorated after dialysis, the amelioration likely to be due to the removal of a dialyzable toxic product that accumulates in uremia [94]. Thus, adequate dialysis treatments may improve platelet aggregation and lower bleeding tendency by removing substances that interfere with fibrinogen-platelet binding and, therefore, platelet aggregation. Removal of toxic products may also improve platelet adhesion to the subendothelium. The often partial character of the response to dialysis implies that patients with high bleeding risk may require further pharmacological therapy.

Recombinant Human Erythropoietin (rHu-Epo)

The hemostatic defect of uremia improves after treatment with rHu-EPO, which transiently raises platelet counts, shortens skin bleeding time, and improves platelet aggregation. Moreover, platelets from patients receiving rHu-EPO therapy appear to be more activated during hemodialysis; such activation could pose problems in terms of dialyzer clotting and arteriovenous fistula thrombosis.

Table 2. Treatment of Uremic Platelet Dysfunction

1.	RBC transfusions Recombinant erythropoietin	Keep HCT > 30% (33 – 36%)
2.	DDAVP[a]	0.3 µgm/kg LV over 15 – 30 mins (in 50 mL saline)
3.	Cryoprecipitate[b]	10 units IV q 12 – 24 hours
4.	Conjugated estrogens[c]	0.6 mg/kg IV daily for 5 days

[a]Useful for acute bleeding before surgery; releases FVIII/vWF from vascular endothelium; onset of action < 1 hour, duration 4 – 8 hours; tachyphylaxis may develop after 1 – 2 doses.
[b]Useful for acute bleeding; risk of viral hepatitis and AIDS; rich in FVIII/vWF and fibrinogen; onset of action 1 – 4 hours, duration 24 – 36 hours.
[c]Not useful for acute bleeding; onset of action in 6 hours with progressive shortening of bleeding time over next 5 – 7 days; duration of action of about 2 weeks; mechanism of action unknown.

rHu-EPO treatment augments the number of GPllb-llla molecules found on the platelet plasma membrane [94]. Administration of rHu-EPO to uremic patients might, therefore, have an impact on thrombopoiesis in addition to erythropoiesis. Consequently, uremic patients with a high frequency of bleeding complications may benefit from appropriate rHu-EPO therapy.

Cryoprecipitate

Cryoprecipitate shortens or normalizes bleeding time in patients with renal failure. The peak effect appears several hours after infusion and persists for 12 – 24 hours. Factor VIII/von Willebrand factor complex (FVIII/vWf) has been shown to play an important role in the pathophysiology of uremic bleeding and it is this component of cryoprecipitate that is postulated to give rise to improved platelet functions in uremia. The delayed onset of action, the short duration of effect, and the risk of contracting infections may limit its application.

Desmopressin (DDAVP)

The importance of FVIII/vWf for uremic platelet dysfunction is substantiated by the fact that 1-deamino-8-D arginine vasopressin (DDAVP) which causes the release of autologous, preformed FVIII/vWf from endothelial storage sites, is effective in the treatment of the bleeding tendency present in patients with acute or chronic renal failure. Bleeding time is improved or normalized one hour after the infusion while the effect of the infusion lasts approximately 4 – 6 hours. The treatment is very well tolerated and has been said to prevent bleeding complications when given prophylactically. Von Willebrand activities rise after DDAVP therapy in the responders but not in the non responders.

Estrogen

Estrogen therapy appears to be effective in improving the bleeding tendency in uremia, although the mechanism of action is unclear. Between 2 – 5 days after beginning estrogen therapy, bleeding time improves or normal-

izes in patients with CRF. After discontinuation of the therapy, the bleeding time remains normal for 3 – 10 days. Although the duration of action compared to that of cryoprecipitate or of DDAVP is longer, the absolute magnitude of the effect on bleeding time may be less.

Seizures on Hemodialysis

The incidence of seizures in patients with ESRD is markedly increased compared to that found in the general population [95, 96]. A number of factors contribute to this increased risk (Table 3) including the neurologic effects of uremia, altered drug kinetics leading to toxicity, the effects of underlying diseases, and metabolic and hemodynamic alterations related to uremia. Dialysis-associated seizures can occur during hemodialysis or following its termination. Hypotension is a frequent cause of seizures and should be avoided and treated accordingly.

Table 3. Etiology of Dialysis-associated Seizures

- Uremic encephalopathy
- Dialysis disequilibrium syndrome
- Hypertensive encephalopathy
- Intracranial hemorrhage
  - Subdural hematoma
  - Intracerebral hemorrhage
  - Ruptured aneurysm (AV malformation in ADPKD)
- Aluminum-related encephalopathy
- Dialysance of anticonvulsant drugs
- Anoxia/ischemia
  - Hypotension
  - Cardiac arrhythmia
  - Anaphylaxis
- Drugs (e.g. penicillins)
- Alcohol or drug withdrawal
- Encephalitis/meningitis
- Vasculitis
- Primary or metastatic intracranial neoplasms
- Idiopathic epilepsy
- Metabolic disorders: hyponatremia, hypernatremia, hypoosmolality, hyperosmolality, hypocalcemia, hypoglycemia, hypomagnesmia, acid-base disturbances
- Air embolism

Uremia

The seizure activity associated with uremia or dialysis tends to be generalized and rarely focal [97]. Presence of focal seizure activity often indicates localized neurologic disease and should prompt an evaluation for presence of intracranial hemorrhage, tumor, localized infection, or other conditions. However, focal seizures may occur with a variety of metabolic disorders (e.g. hypoosmolality or hyperosmolality, hypoglycemia) and hypertensive encephalopathy in dialysis patients, in the absence of discernible lesions.

It is important to distinguish true seizures from metabolic or toxic myoclonus. The generalized convulsive movements of major motor seizures (grand mal) involve large proximal muscle groups, are usually rhythmic, bilaterally symmetric, and associated with loss of consciousness and post-ictal confusion. In contrast, uremic myoclonus is typically a multifocal, nonpatterned twitching of the muscle groups of the face and extremities with no loss of consciousness.

Recombinant Human Erythropoietin (rHu-EPO)

RHu-EPO, commonly used for treatment of renal anemia, has been reported by some to increase the incidence of seizures. These seizures are usually associated with rHu-EPO

induced new onset hypertension or exacerbation of preexisting hypertension. The risk of seizure is greatest during the first few months of therapy, when the drug dosage is usually highest, the rise in erythrocyte mass is greatest, and platelet count is increased. It should be noted, however, that most studies have failed to demonstrate a consistent relationship between changes in blood pressure and the rate of increase in the hematocrit during rHu-EPO therapy. These observations, along with demonstration of increased isolated vascular smooth muscle tone in the presence of erythropoietin in vitro, have lead to speculation that erythropoietin may have a direct effect on vascular resistance and cerebral blood flow [98, 99].

The risk of seizures during rHu-EPO therapy can probably be minimized by dosing the drug in a manner as to produce a slow, gradual rise in hematocrit. In addition, meticulous monitoring of blood pressure and prompt initiation of adjustment of antihypertensive therapy, when indicated, is essential [100]. It should be noted that several recent large series have failed to show a significant association between rHu-EPO therapy and seizure disorders [98].

Aluminum Encephalopathy

Aluminum toxicity (dialysis dementia, dialysis encephalopathy) may occur with the use of aluminum-contaminated dialysate or extended use of aluminum-containing phosphate binders [101]. Routine treatment of water supplies to maintain the dialysate aluminum concentration <10 µg/L has largely eliminated dialysate as a source of aluminum. Moreover, widespread use of calcium-containing phosphate binders has reduced long-term aluminum accumulation. Patients with aluminum toxicity typically exhibit dementia, speech disturbances, apraxia, myoclonus, facial dystonia, and sometimes seizures. In addition, other manifestations of aluminum toxicity including erythropoietin-resistant microcytic anemia, hypoplastic bone disease, hypercalcemia, and depressed PTH levels may be present [101]. Although blood aluminum concentration is usually greater than 50 µg/L in symptomatic cases, aluminum concentration does not always correlate with clinical symptoms [102].

Management

Dialysis should be stopped. Patency of airway and avoidance of aspiration are of immediate concern in the management of seizures occuring during dialysis. Hypotension should be checked, and if present, treated promptly. Blood lines should be checked for air embolism. Supplemental oxygen administration should be considered, especially in patients with underlying cardiac or pulmonary dysfunction. In patients with chronic obstructive lung disease, high concentrations of oxygen (> 24%) should be avoided to prevent hypercarbia. Blood should be sent immediately for glucose, calcium and electrolyte determinations. If hypoglycemia is suspected, dextrose 50% should be administered. If seizures persist after correction of hemodynamic and metabolic abnormalities, specific anticonvulsant therapy should be considered. Intravenous diazepam (5 – 10 mg) can be given every 5 minutes to a maximal dose of 30 mg to terminate the seizure. Phenytoin can then be given at a loading dose of 10 – 15 mg/kg by a slow IV infusion (not to exceed 50 mg/min) and with constant ECG monitoring.

When using antiepileptic drugs, knowledge of their altered pharmacokinetics in ESRD and their dialysance is essential. Phenytoin is normally 90% protein bound with a volume

of distribution (V_d) of 0.6 L/kg and a half-life ($t^{1/2}$) of 18 hours [103]. In ESRD, protein binding is decreased, V_d is increased, and its half life decreases to 8 hours. Normal therapeutic range of *total* drug is 10 – 20 mg/mL. Normally, the unbound fraction is 0.1 of total; hence the *free* (unbound fraction) drug level associated with optimal treatment is 1 – 2 µg/mL. In uremia, the unbound protein fraction can increase to 0.3 total. Consequently, in uremia a total drug concentration of 5 – 10 µg/mL is considered therapeutic and this level will lead to a therapeutic unbound fraction of 1 – 2 µg/mL. Drugs known to displace phenytoin from plasma protein binding sites include valproic acid, non-steroidal antiinflammatory agents (NSAIDs), and salicylic acid. Finally, phenytoin follows first-order kinetics. Increases in dosing should be small, and sufficient time should be allowed to achieve a new steady state. The altered protein binding and shortened half-life of phenytoin necessitates an additional adjustment in dosage schedule in uremia, namely to give phenytoin in divided dosage (TID schedule).

Prevention

To lessen the risk of seizure activity on dialysis, particularly in predisposed patients, the following measures should be observed:

- if a patient is known to be on anticonvulsant drugs, give an additional dose postdialysis if the drug is dialyzable. Anticonvulsant drugs that are not dialyzable include diphenylhydantoin and carbamazepine. Valproic acid may be partly dialyzable. Dialyzable drugs that need supplemental dose post dialysis include phenobarbital, ethosuximide, trimethadione, and paraldehyde.
- In severely hypocalcemic patients, especially in the presence of severe metabolic acidosis, consider calcium treatment even before dialysis;
- anticipate and avoid conditions associated with dialysis disequilibrium syndrome (see below); and
- drugs that may have untoward CNS effects in uremia should have careful dose adjustment. These include penicillins, cephalosporins, nitrofurantoin, isoniazide, meperidine, morphine, cimetidine, phenothiazines, haloperidol, barbiturates, benzodiazepines, antihistamines, hypoglycemic agents, methyldopa, β-adrenergic antagonists, cyproheptadine, anticoagulants, and neuromuscular blocking agents.

Dialysis Accidents

Erroneous Temperatures

Dialysate temperature, normally set at 37° C, is regulated by a thermostat, a component of the dialysate temperature monitoring system. Malfunctions of the thermostat or of the other components of the monitoring system can result in abnormal dialysate temperatures. Although a cool dialysate (e.g. 34.5° C) has been used to promote vasoconstriction to maintain an adequate blood pressure during dialysis, too low a temperature can bring about shivering and increased secretion of catecholamines.

High dialysate temperatures lead to cutaneous vasodilatation, sweating, and a sensation of warmth. For the conscious patient, overheating is often detected before a dangerous elevation in body temperature makes its appearance. If dialysate temperature is allowed to rise to 55° C or higher, massive hemolysis with resultant hyperkalemia [104] and death can take place. Delayed hemolysis has been

observed with intermediate temperatures. This delay is related to splenic trapping and peripheral destruction of the damaged erythrocytes.

Treatment for hemolysis requires the immediate cessation of dialysis, the discard of blood present in the extracorporeal circuit and the transfusion of blood in case anemia is severe. Hyperkalemia should be treated by the usual means, not the least of which is another dialysis treatment using functional equipment and potassium-poor or potassium-free dialysate.

Air Embolism

Air embolism is one of the dreaded complications of hemodialysis and the extracorporeal system is designed with redundant safeguards to avoid its occurrence. It is important, however, to maintain vigilance as human and technical failures are always possible. It can occur either as a result of the manipulation of the extracorporeal circuit, or as a complication of a temporary vascular access placement procedure. Venous air embolism, however, remains an infrequent complication. The cardiovascular, pulmonary, and central nervous systems may all be affected, with severity ranging from absence of symptoms to immediate cardiovascular collapse. Symptoms and signs attributable to air embolism can take place with small volumes of air entering the patient's circulation. While it is difficult to quantitate the amount of air in clinical settings, experimental studies suggest that the introduction of 1 mL/kg may be fatal.

The manifestations of air embolism depend on the posture of the patient and the flow of air obeys the law of gravity. In the sitting position, air will flow along the venous system to reach the central circulation and then will backflow into the cerebral venous system. The patient will transiently be aware of the sound of the air in his vessels and then will lose consciousness and develop seizures. In recumbent patients, air will reach the right atrium and the right ventricle, with the developing air-blood foam occluding the right ventricular outflow tract and the pulmonary vascular bed. Chest pain and shortness of breath appear, followed by cardiovascular collapse.

Venous air embolism can occur during the insertion, the disconnection or the removal of a central venous catheter [105]. Air embolization through a residual track after removal of a central venous catheter, particularly after long-term catheterization or repeated use of the same puncture site, is an elusive mechanism that while rare, can be recognized only if searched for carefully.

Venous air embolism induces rapid hemodynamic changes, most notably a sharp increase in central venous pressure. In addition to the obstructive element, pulmonary vasoconstriction modulated by the action of the platelet activating factor, also takes place. Pulmonary edema can set in. Entry of air into the pulmonary arterial tree causes physical obstruction of the microvasculature and leads to permeability changes, release of mediators, and injury to lung tissues. In addition to its hemodynamic consequences, air in the circulating blood activates complement in a dose-dependent fashion [106].

Air in blood vessels can be visualized by real time ultrasonography and air volume, estimated by a doppler [107]. Therapeutic interventions include mechanical measures, such as positioning, withdrawal of air from the right atrium, and means aimed at reducing bubble size. Speed in therapy is essential. The blood lines should be clamped and the patient rapidly positioned in the Trendelenburg position with the left side down. This posture reduces the movement of air to the brain and traps the air bubbles in the right ventricle. This

air trapping minimizes foaming which ordinarily takes place also mainly in the right ventricle. In this position, air may even migrate to the periphery; such air migration can be detected by the development of patchy cyanosis over the lower extremities. While migration of the air may affect distal sites, it is clearly less catastrophic than having air in the central circulation or in the cerebral vessels.

Hyperbaric oxygen therapy holds some promise in accomplishing reduction of air bubble size [108]. Even after a prolonged delay, patients with cerebral air embolism may still benefit from hyperbaric oxygen therapy. Even normobaric oxygen may be useful, particularly if mechanical ventilation is employed. Experimental studies suggest that the removal rate of air from cerebral vessels is dramatically enhanced by mechanical ventilation at partial pressure of oxygen (F_iO_2) of 1.0 [108]. The prompt application of mechanical ventilation with an F_iO_2 of 1.0 is recommended when air embolism is suspected particularly in centers where facilities for administering hyperbaric oxygen therapy are not available.

While prevention and early diagnosis represent the cornerstones of management, definitive therapy of a massive air embolus may require aspiration of the air through an appropriately located multi-orifice catheter. Throughout management, the patient should be moved as little as possible.

Dialyzer Rupture or Clotting

Dialyzer rupture is a rare event in hemodialysis. It is usually detected by an alarm which is triggered by the presence of very low concentrations of blood in the dialysate. A variety of factors predisposes to this complication; such factors include faulty construction, high venous pressures secondary to clotting or kinking of blood lines, and improper priming. While most ruptures result in the loss of only a small amount of blood and may seal spontaneously, the potential for massive blood loss requires that immediate remedial measures be taken. Septicemia is also a risk. The blood lines should be clamped, the patient disconnected from the extracorporeal circuit and the latter completely changed. Moreover, the dialysate circuit and the blood leak detector will need to be cleaned.

Dialyzer clotting is a more common event and is usually due to inadequate heparinization. This, however, cannot be the sole cause as hemodialysis without anticoagulation is readily performed with either intermittent or continuous saline rinsing. Additional factors include a high venous pressure, a low blood flow, a large amount of air in the drip chambers or in the dialyzer headers because of poor attention to proper rinsing procedures prior to starting dialysis. Furthermore, rapid connection of the patient to the extracorporeal circuit immediately after heparin administration without allowing for systemic anticoagulation to begin taking effect may be contributory.

Dialysis Disequilibrium

Clinical Features

This dialysis-induced syndrome consists of a constellation of manifestations including mental confusion or agitation, nausea, vomiting, headache, drowsiness, lassitude, confusion, muscle twitching, delirium, seizures and coma. In severe cases, there is an rise in blood pressure, pulse rate and respiratory rate. Occasionally, death can occur [109, 110]. In addition, characteristic electroencephalographic (EEG) abnormalities in the form of

high-voltage rhythmic delta waves are commonly encountered.

The syndrome is more likely to develop when the initial plasma urea level is markedly elevated and correction of the azotemia is rapid. Therefore, the syndrome is encountered mostly in the early stages of dialysis therapy when plasma urea level often is highest, but may recur even after many months of dialysis should the patient raise his protein intake. The syndrome is frequently seen toward the end of a dialysis session and usually transient, lasting for 24 hours after the termination of dialysis. A predisposing factor for the development of the syndrome is a preexisting neurologic disorder [109].

Pathophysiology

The exact pathogenetic mechanism for the dialysis disequilibrium syndrome is not fully understood at present. What is known for certain is that there is evidence of cerebral swelling. There are several theories concerning the pathogenesis of the dialysis disequilibrium syndrome, the most popular being the 'reverse urea effect' theory. In this theory, the intracellular water gain is believed to be a result of a dialysis-induced lowering of the plasma urea level in the presence of a lesser fall in intracellular urea concentration [109, 110]. This urea gradient implies the slower passage of urea out of brain tissue and the consequent transfer of water from the blood to the brain. Furthermore, the suppression of dialysis-induced EEG abnormalities by the use of a urea-enriched dialysate adds weight to the 'reverse urea effect' contention. In a similar vein, clinical manifestations associated with the dialysis disequilibrium syndrome can be ameliorated by maintaining plasma osmolality with the use of a high-sodium dialysate [111]. Recently, the concept of the 'reverse urea effect' has received additional support from the finding of an elevation in brain water and a rise in the brain-to-plasma urea ratio in azotemic rats subjected to acute hemodialysis treatments [112].

Management

The syndrome is rarely seen when a moderately elevated plasma urea nitrogen level (e.g. 29mmol (80 mg/dL)) is lowered by conventional or high-efficiency dialysis (e.g. to 15mmol (40 mg/dL)). Moreover, it is best to initiate dialysis long before azotemia becomes extreme and with current recommendations for initiation of dialysis at residual renal function levels of 10 – 15 mL/min of GFR, the syndrome should become a rarity. In the event that dialysis is required in a patient with an extremely raised plasma urea nitrogen value, an inefficient dialysis treatment can be delivered by shortening the duration of a dialysis run to 25 – 40% of the normal, by lowering dialyzer blood or dialysate flow rates, or by using a less efficient dialyzer. If no untoward effects appear, the efficacy of the subsequent daily dialysis treatments can be lengthened in a step-wise manner over the next several days until regular dialysis treatments can be safely delivered.

Prophylactic administration of osmotic agents such as glucose, mannitol, urea and sodium chloride either IV or via the dialysate route, with the aim of reducing the incidence of the dialysis disequilibrium syndrome has been recommended [111]. However, since modern dialysis machines can raise dialysate sodium levels readily, use of a high sodium dialysate may be the most convenient approach. Once the dysequilibrium syndrome sets in, treatment will be symptomatic. Seizures can be treated with intravenous diazepam, with effects lasting 30 – 60 minutes.

When compared to barbiturates, diazepam causes less respiratory depression. Short-acting barbiturates can also be given but are more dangerous since they can cause more respiratory depression. It should be noted that even though diazepam and some related drugs are metabolized by the liver, great care should be exercised in their use since many renal failure patients cannot tolerate the dosages ordinarily recommended for patients with normal liver and renal functions.

Electrolyte Abnormalities

Metabolic Alkalosis

Metabolic alkalosis as a consequence of intensive dialysis (e.g. daily dialysis) using a dialysate with a high level of buffer base (e.g. 40mmol), is rarely described. What is more often encountered, however, is metabolic alkalosis developing as a complication of hemodialysis employing sodium citrate as a means of regional anticoagulation [113]. The infused citrate is converted into bicarbonate by the body. In some regional anticoagulation regimens, citrate concentrations of 7mmol have been found in afferent blood, resulting in severe metabolic alkalosis. Prevention requires employing as small an amount of citrate as possible. Should reduction in citrate administration be impossible, the level of buffer base in the dialysate can be curtailed. Severe metabolic alkalosis can be treated, if desired, by hemodialysis using a low buffer-base and high chloride dialysate.

Metabolic Acidosis

Metabolic acidosis can develop if the delivery of buffer base to the dialysate in the form of sodium acetate or sodium bicarbonate is defective [114, 115]. For instance, the single 'acetate concentrate' meant for dilution with water to form an acetate-based dialysate can be accidentally replaced by the 'acid concentrate' component of a two-component, bicarbonate-based dialysate generating system. This can occur in units that continue to practice both types of buffer delivery. This 'acid concentrate' contains sodium, potassium, calcium, magnesium, chloride, glucose and acetic acid. Since this concentrate is devoid of buffer base, its use would bring about metabolic acidosis as a result of the removal of bicarbonate from the blood by dialysis. Another way for metabolic acidosis to set in during dialysis involves the faulty delivery of a buffer base-containing concentrate. For example, the tube responsible for the siphoning off of a 'bicarbonate concentrate' can be damaged [115]. A third way for metabolic acidosis to develop centers on the presence, in the dialysate, of too much water in relation to the available buffer base (an example of dilution acidosis). Treatment of the acidosis comprises the administration of sodium bicarbonate, or of a properly performed acetate- or bicarbonate-based dialysis session using appropriate and functional equipment.

Hyponatremia

Inadvertent use of a markedly hyponatric dialysate during dialysis can occur if conductivity limits of the dialysis machine are not adjusted appropriately such that abnormal proportioning among concentrate(s) and product water are left undetected. Use of such hyponatric dialysates can bring about hyponatremia as a result of the removal of sodium from, and the introduction of water into, the body. The resultant plasma hypoosmolality causes water to enter the intracellular space

leading to water intoxication, cerebral edema and hemolysis. Clinical manifestations include abdominal pain, diarrhea, leg cramps, hypertension, Kussmaul breathing, apprehension, coma, and other neurological disturbances. Hyperkalemia can occur because of the hypoosmolality-induced hemolysis while metabolic acidosis can take place because of dilution of plasma bicarbonate by dialysate water and loss of plasma bicarbonate into the dialysate. Treatment consists of cessation of the current dialysis run, initiation of another dialysis treatment using sound equipment and proper dialysate. Since the onset of the hyponatremia is abrupt, rapid correction of the hyponatremia with hypertonic saline infusion, is justified in order to reduce the degree of cerebral edema [116]. However, serum sodium level should not be brought back to a level higher than 120 – 125mmol or so initially. Blood transfusion should be given if the anemia is severe. Prevention of dialysis-associated hyponatremia depends on meticulous attention to details in the preparation of dialysate and the frequent monitoring of dialysate conductivity value.

Hypernatremia

Dialysate sodium concentrations can be abnormally raised as a consequence of technical failures in water or concentrate pumps or if the conductivity sensors are defective. The hypernatremia can abstract water into the extracellular space from the intracellular compartment causing cellular (including cerebral) dehydration. In those situations in which a hypernatric dialysate is used, extracellular fluid volume may not be elevated because water is also being lost to the dialysate. CNS manifestations such as headache, disorientation, seizures, spasticity and coma are frequently encountered. Other symptoms include nausea, vomiting, hot flushes, weakness, and profound thirst. Death can result.

Treatment consists of discontinuation of the current dialysis session, drinking of water, IV administration of 5% glucose water, and dialysis with a dialysate containing appropriate levels of sodium. The rate of fall of plasma sodium permitted should be guided by the general guidelines for the treatment of acute hypernatremia.

Hypokalemia

Renal failure patients who are dialyzed against a very low-potassium or a potassium-free dialysate can develop hypokalemia and intracellular potassium depletion due to loss of potassium into the dialysate [117]. This complication can take place even in the patient with predialysis hyperkalemia. Patients who are hypokalemic are at risk of developing cardiac arrhythmias, including premature ventricular contractions (PVC) and ventricular fibrillation. In addition, hypotension, fatigue, muscular weakness and paralysis can occur.

Acute lowering of serum potassium engenders a high ratio between intracellular and extracellular fluid potassium concentration, resulting in a more negative resting membrane potential and, hence, a hyperpolarization block. Coronary artery disease, hypertensive cardiovascular disease, digitalis therapy, hypercalcemia, hypomagnesemia and metabolic alkalosis predispose to this hypokalemia-induced cardiac arrhythmia. Patients entering dialysis with a history suggestive of prolonged potassium loss, marked metabolic acidosis, moderate hypokalemia or normokalemia are especially vulnerable to this complication.

Intensive dialysis in an average dialysis patient without severe metabolic acidosis can

bring about a metabolic alkalosis with resultant hypokalemia even if a normal potassium dialysate is used. In such patients, the dialysate buffer base level should be lowered appropriately. Proper attention to dialysate potassium levels will prevent many of these complications.

In patients prone to have dialysis-associated cardiac arrhythmias, special precautions are necessary. Raising dialysate potassium reduces the frequency of arrhythmias in those patients who suffered from arrhythmias while being dialyzed with low potassium dialysate. This reduction, however, results in higher predialysis serum potassium value of the succeeding dialysis treatment.

Hyperkalemia

Hyperkalemia occurs commonly in dialysis patients with dietary indiscretion. Dialysis-induced hyperkalemia occurs with hemolysis. Intradialytic hemolysis has been reported following accidental exposure to overheated or hypotonic dialysate, chloramine, formaldehyde, nitrate, copper, and sodium hypochlorite. Another rare cause for the development of hyperkalemia is dialysis with fluoride-contaminated dialysate [118]. Iatrogenic hyperkalemia could occur if a dialysate with an inordinately high potassium level were inadvertently used.

Hypophosphatemia

Hyperphosphatemia is almost a universal finding in ESRD patients because of the intermittent nature of phosphate removal during hemodialysis. Dialysis-induced hypophosphatemia develops under unusual situations such as:

- intensive (e.g. daily) dialysis for patients suffering from dialysis pericarditis;
- thrice weekly regular dialysis treatments in patients with poor dietary intake either because of intercurrent illness or failure to thrive. Dialysis-induced hypophosphatemia can also be seen in patients with normal renal function who are dialyzed because of intoxications with poisons such as lithium. Therapy of such intoxications often focuses on prolonged and repeated dialysis treatments. Hypophosphatemia may develop in these patients because of the removal, by dialysis, of phosphorus from their bodies whose phosphorus contents are not elevated to start with on account of the presence of normal renal function.

Hypophosphatemia causes dysfunction of erythrocytes, leukocytes, platelets, the CNS, skeletal and cardiac muscles as well as the skeleton. However, hypophosphatemic manifestations are usually mild unless serum phosphorus level falls below 0.33mmol (1.0 mg/dL). Treatment of hypophosphatemia centers on the ingestion of phosphorus-rich food (such as skim milk) and of phosphorus salts (such as sodium or potassium phosphate), and, in severe cases, the IV administration of sodium or potassium phosphate. Dialysis-related hypophosphatemia can be prevented by the use of a phosphorus-enriched dialysate.

Hypercalcemia and Hypermagnesemia

Dialysis against a conventional 1.32mmol calcium dialysate can raise plasma calcium concentrations of dialysis patients from a predialysis value of 2.28mmol to a post-dialysis

level of 2.45mmol [119]. This dialysis-induced hypercalcemia is partly due to an increase in plasma protein concentrations brought about by the loss of a protein-free fluid from plasma as a result of ultrafiltration. The rise in plasma protein level is accompanied by a corresponding increase in the protein-bound fraction of plasma calcium [120]. In addition, the small intradialytic gain of calcium by the body from the dialysate also contributes to the hypercalcemia. Dialysis-induced hypercalcemia is transient in nature and does not lead to symptoms. No treatment is required.

In the recent past when aluminum-containing phosphate binders were used, a dialysate calcium level of 1.75mmol was the standard dialysate calcium concentration used in most dialysis centers. With the replacement of aluminum hydroxide by calcium salts (such as calcium acetate or carbonate) as phosphorus-binders and the widespread use of calcitriol and related compounds to combat renal osteodystrophy, hypercalcemia is not uncommonly encountered if a dialysate calcium level of 1.75mmol is used [121]. Because of the above reasons, dialysate calcium level is nowadays often lowered to 1.0 – 1.25mmol to discourage the development of hypercalcemia.

Treatment for this type of hypercalcemia consists of ingesting calcium-containing phosphorus binders only during meals so that the calcium administered will combine with the phosphorus present in food to form insoluble calcium phosphates. In addition, vitamin D therapy should be discontinued. Aluminum toxicity, if present, should be promptly treated. A dialysate containing an appropriately low level of calcium should be employed. If the use of a low dialysate calcium is unsuccessful, alternate methods are available. Pamidronate, a drug that reduces osteoclast-induced resorption of bone and curtails transformation of osteoclast precursors into mature osteoclasts, has been used successfully to control the present variety of hypercalcemia [122].

In many parts of the world, water intended for consumption often has very high concentrations of calcium and magnesium [123]. Specifically, the levels of calcium and magnesium in such water have been found to reach values as high as 2.0 and 0.95mmol respectively [123]. Should the means of purification of such water (e.g. water softener or deionizer) for the purpose of dialysis be faulty, a patient could be exposed to inordinately elevated dialysate levels of the divalent cations, resulting in what is known as the “hard-water syndrome”.

Patients suffering from the “hard-water syndrome” often complain of nausea, vomiting, general malaise, somnolence, weakness, sweating, warm skin sensation, abdominal pain, tachycardia, hypertension or hypotension. In addition, neurological manifestations in the form of headaches, dysarthria, seizures and myoclonic jerks are common. Mental abnormalities such as hallucinations, confusion, memory loss and judgment defects can occur.

Treatment for hypercalcemia or hypermagnesemia as a consequence of the inadvertent use of high-calcium and/or high-magnesium dialysate centers on the use of a dialysate containing appropriate amounts of the divalent cations.

Contamination of Dialysate Water

Fluoride

Dialysis patients are particularly susceptible to fluoride intoxication due to their repeated exposures to the large volumes of water in the course of dialysis (120 L per

dialysis session; 19,000 L per year of maintenance hemodialysis) and to their lack of the usual renal route of fluoride excretion. Since fluoride has a molecular weight of only 19 daltons, it is readily transferable into the blood from the dialysate. Although municipal water generally contains in the realm of 53 micromolar fluoride, product water used for preparing dialysate should have a fluoride level less than 11 μM (i.e. < 0.2 parts per million (ppm)) [124]. In general, properly reverse osmosis-treated and deionized water can more than meet this requirement. Faulty reverse osmosis and deionization systems can result in contamination of product water by fluoride [124]. Continued use of the exhausted resins to treat municipal water causes low-affinity anions, such as fluoride, already bound to the resins, to be displaced into the effluent by higher-affinity anions, such as nitrate, sulfate, and chloride. As a consequence, a patient can be exposed to a dialysate fluoride level as high as 1,000 μM [118]. Finally, a rare cause for a high level of fluoride in dialysate is the accidental gross contamination of municipal water with fluoride-containing compounds while reverse osmosis and de-ionization equipment is not being utilized [125].

The toxicity of fluoride is related to its ability to oxidize other chemicals and to combine with organic compounds, resulting in a direct interference with various cellular metabolic processes. In addition, fluoride, being the most electronegative element, can readily bring down the serum levels of calcium and magnesium because of its tight binding with these cations.

Because a period of fluoride accumulation is necessary to incite patient responses, the onset of clinical manifestations can be anticipated to take place late into, or soon after dialysis [118]. Many patients in the same dialysis unit (if they share the same source of product water) are likely to demonstrate similar signs and symptoms at approximately the same time [118]. Early symptoms include nausea, vomiting, pruritus, burning or feverish feeling, headache, syncope, back or abdominal pain, diarrhea, chest pressure or pain, cardiac irritability and bradycardia. Later on, binding of blood calcium by fluoride can bring about generalized muscle twitching, tetany, petechiae and bleeding from vascular access puncture sites. Still later, respiratory failure, hypotension, seizure, coma, cardiac arrest, and death can occur [125]. Treatment of acute fluoride poisoning entails the immediate cessation of the current dialysis; intravenous administration of calcium salts, sodium bicarbonate, glucose and insulin (for the therapy of hyperkalemia, acidosis and hypocalcemia if these abnormalities are present); and prompt dialysis using a bicarbonate-based, zero to normal potassium and fluoride-undetectable dialysate. Multiple or prolonged dialysis treatments may be required to remove adequate amounts of fluoride from the body. Should hemodialysis using fluoride-undetectable dialysate be unavailable, peritoneal dialysis should be instituted. Prevention of fluoride toxicity involves the meticulous purification of product water, frequent measurement of the fluoride concentration in product water and the ensuring of proper functioning of the reverse osmosis and the de-ionization systems.

Methemoglobinemia

When the ferrous ion that is attached to the heme of hemoglobin is oxidized to the ferric form by an oxidizing agent, a derivative of hemoglobin known as methemoglobin, is produced. Methemoglobin is without function because its heme molecule cannot bind oxygen. Dialysis-associated methemoglobinemia

can occur as a result of exposure to oxidizing agents such as:

Nitrate

Patients who are dialyzed with nitrate-rich well water can develop methemoglobinemia [126]. Wells that are poorly constructed or poorly located may have a high level of nitrates in their water due to seepage of wastes. Prevention of the present methemoglobinemia depends on the removal of nitrites from product water by means of a de-ionizer. When the methemoglobinemia is mild, no treatment is necessary since the methemoglobin will be spontaneously reduced to hemoglobin by the body over 2 – 3 days. For severely affected patients, l – 2 mg/kg of a 1% solution of methylene blue in saline is administered IV over 10 minutes. A second dose can be repeated in an hour if needed.

Chloramine

Chlorine is often used as a disinfectant for municipal water supplies. However, chloramines, compounds composed of chlorine and ammonia, are increasingly considered to be environmentally safer alternatives to chlorine for disinfecting water supplies [127]. This is because chloramines are less volatile and have a less objectionable smell and taste than chlorine. Furthermore, unlike chlorine chloramines do not react with naturally occurring organic compounds to form chloroform. For the purpose of dialysis, municipal water treated with chloramines is ordinarily purged of these disinfectants by passage through charcoal filters (also known as carbon filters) containing granular activated carbon particles [128].

In case the delivery of municipal water to a charcoal filter is excessive in relation to the capacity of the filter to remove chloramines, that particular filter can become prematurely exhausted and allow chloramines to enter and contaminate the product water. Drought conditions require the use of larger amounts of chloramines because drought-induced stagnation of water encourages bacterial and fungal growth. The greater quantity of chloramines added may tax the capacity of existing filters to remove these disinfectants.

According to Association for the Advancement of Medical Instrumentation (AAMI) standards, product water geared for dialysis should not have a chloramine level higher than 0.1 mg/L (0.1 ppm) [129]. High blood levels of chloramines can oxidize the hemoglobin in the blood to form methemoglobin and Heinz bodies, the latter being intracellular precipitates of denatured hemoglobin. Red cells exposed to chloramines are very susceptible to hemolysis and a hemolytic anemia is readily encountered.

The hemolytic anemia due to exposure to chloramines can be severe enough to warrant blood transfusion. Prevention consists of routing municipal water through appropriate charcoal filters [129], with the realization that chloramines are not removed by reverse osmosis. The American Food and Drug Administration (FDA) recommends that 2 charcoal filters be used in series for a water treatment system. A systemic plan for replacing the filters as they become exhausted should be established. Exhausted charcoal filters should be replaced with fresh ones, and should not be rejuvenated by backwashing. Although backwashing may loosen the packed carbon particles and restore surface area, it does not remove previously aggregated material from the charcoal and, therefore, does not regenerate the filter [127]. In order to ensure the absence of chloramines, product water should be tested for the chemicals at least once per patient shift to ensure patient safety [129].

Addition of vitamin C, a reducing agent, to a dialysate at a concentration of 17 – 34 mg/L

has also been found to be effective in converting dialysate chloramines to the relatively innocuous ammonium chloride, whether the batch method or the proportioning method of producing dialysate is used [130]. It should be emphasized that patients who are dialyzed with vitamin C-enriched dialysate should not take oral vitamin C supplements. This approach of enriching dialysate with vitamin C will only result in serum levels approximating those seen in maintenance dialysis patients taking standard oral vitamin supplements. Some centers employ both charcoal filters and vitamin C enrichment at the same time.

Miscellaneous Complications

Febrile Episodes and Endotoxin

Pyrogenic episodes associated directly with hemodialysis treatments are infrequent [131] and their presence should always elicit a search for underlying bacterial infections [132]. Occasionally, clustering of febrile episodes, particularly after any mechanical work on the water supply system, raises the possibility of contamination. Bicarbonate dialysate concentrates can support bacterial growth with endotoxin production. Endotoxins or bacteria may cross or interact at the membranes of high-flux dialyzers, triggering the release of endogenous pyrogens (e.g. certain cytokines) by peripheral blood mononuclear cells to cause pyrogenic reactions. Pyrogenic reactions occur at a rate of 0.7 reaction per 1,000 hemodialysis treatments [133]. This incidence is not different between conventional, and high-flux or high-efficiency modalities of dialysis [133].

Pyrogenic reactions occurring in clusters are more frequently reported in centers that reuse conventional dialyzer membranes compared to centers that do not [134 – 136]. Use of dialyzers with detachable components such as headers has been associated with an increased incidence of infections (e.g. 'header sepsis') with a variety of organisms including Xanthomonas, and other slow-growing organisms, a problem that can be solved with proper disinfections of the O rings and other components of the header [137, 138]. Improper preparation of the disinfectant has also been associated with clusters of infection with Pseudomonas species [139]. Nontuberculous mycobacteria are ubiquitous in municipal water and outbreaks of infection with these organisms during reuse have been reported. Because of the organisms' greater germicide resistance compared to that of most other naturally occurring water bacteria, attention to the quality and concentration of disinfectants is mandatory.

The minimal dose of endotoxin necessary to induce fever in man (5 ng/kg; 1 ng corresponds to 10 endotoxin units) can be readily achieved in some contaminated dialysates. Levels > 100 EU/mL have been found in up to 10% of German dialysis units surveyed [140].

Endotoxin transfer may contribute to cytokine induction. While the clinical significance of the latter phenomenon remains unknown, the use of ultrapure water has been reported to result in a reduction in the prevalence of the carpal tunnel syndrome [141]. In examining for endotoxemia in dialysis patients, care should be taken to use the proper test. The limulus amebocyte lysate-reactive material (LAL-RM) is cellulose-derived and cross-reacts with LAL via factor G. Using the conventional chromogenic limulus test, all patients treated with regenerated cellulose dialyzers will show elevated values. In this setting, a specific endotoxin assay with factor G-free LAL should be used.

Dialysis-Associated Catabolism

Hemodialysis is considered to be a catabolic event, increasing urea generation rate during dialysis and leading to a negative nitrogen balance. A major contributory factor to this event is the loss of amino acids during dialysis ranging between 6 – 13 g per dialysis session. This loss in amino acids via the dialysate leads to a decline in arterial amino acid concentrations and a concomitant rise in efflux of amino acids from tissue, mainly skeletal muscle. This phenomenon does not appear to be related to the presence or absence of glucose in the dialysate (or conversely the gain or loss of glucose) [142]. This effect appears to be dialyzer membrane-dependent, being greater with high-flux membranes, and still greater with the reuse of such membranes. Reuse of high-flux dialyzer membranes also appears to augment albumin losses during dialysis. After the 20th reuse, the loss of albumin can reach 10 g per session [143].

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Complications of Peritoneal Dialysis

Martin J. Schreiber, Jr.

Introduction

Patients with chronic disease have an increased risk over time to develop medical and/or surgical complications related to either the underlying disease or its treatment. These disease complications can have a significant impact on overall patient morbidity and survival. Currently an estimated 120,000 patients utilize peritoneal dialysis (PD) for the treatment of end-stage renal disease (ESRD) worldwide. Even though the actual percent of patients treated with PD differs by country (England 48%, US 14 %, Japan 6%, Australia 31%, France 10%), similar modality-specific complications may occur. Table 1 summarizes a wide range of modality-specific or organ-system complications that have been reported in patients on PD. Patient survival varies by complication rate, age, presence of diabetes mellitus (DM), and systemic competing risks; these characteristics vary by country and sociodemographic group. Peritonitis remains the major cause of drop out from PD programs. Infectious complications account for 43 – 50% of all patient admissions, 36.3% of hospital days, 22% of catheter complications, and 19.8% of technique-related complications. Various additional complications may be related directly or indirectly to the actual dialysis technique. Complications result in a higher rate of hospitalizations, greater length of stay and post hospitalization morbidity. Strategies to anticipate complications in the outpatient setting which significantly increase the risk for hospitalization should be developed.

Table 1. System Categories for Complications of Peritoneal Dialysis (events, clinical/laboratory findings) and Hospitalization Complications

1. Technique-specific/Non-infectious
- Membrane failure: true and apparent
- Sclerosing encapsulating peritonitis (SEP)
- Catheter-related: placement, hernia, malfunction, leak, perforation, other
- Hemoperitoneum
- Dialysis-related pain syndrome: inflow, outflow, generalized

2. Infections
- Peritonitis: typical organisms, atypical organisms, eosinophilic, sterile
- Catheter exit site (CESI): acute, chronic, tunnel, trauma
- *S. aureus* nasal carriage
- Antibiotic toxicity (gentamicin, vancomycin, quinolones)
- Vancomycin-resistent enteriococci (VRE)

Table 1. continued

3. Cardiac/Vascular
– Myocardial structural abnormalities (left ventricular hypertrophy, systolic dysfunction, infarction)
– Valvular abnormalities and calcification
– Arrhythmias
– Atherosclerosis: hyperlipidemia: cholesterol, triglyceride, Lp(a), homocysteinemia
– Abnormal vascular pro-ischemic factors
– Vascular calcification
– Vascular disease patterns: central, peripheral, cerebral
– Blood pressure: hypotension/hypertension
– Autonomic insufficiency
– Pericardial abnormalities: infection, inflammation

4. Musculoskeletal
– Hypocalcemia, hypercalcemia, hyperphosphatemia
– Low-turnover bone disease (adynamic bone disease)
– Dialysis-associated amyloid: B2 microglobulin amyloidosis, cervical spondoarthropathy
– Erosive azotemic arthropathy
– Osteopenia, abnormalities in mineral density/flouride
– Carpal tunnel syndrome
– Myopathy
– Extraskeletal calcification: periartcular, soft tissue
– Back pain
– Other: tendonitis, tendon rupture, capsular tear, inflammation, fluoride abnormality
– Oxalate abnormalities

5. Pulmonary
– Hydrothorax
– Respiratory function abnormalities
– Bronchopulmonary infections
– Metastatic pulmonary calcification
– Pulmonary edema
– Sleep-related respiratory disorders

6. Metabolic
– Acid-base abnormalities: lactic acidosis, metabolic acidosis
– Electrolyte/mineral disorders: hypokalemia, hypophosphatemia, hypomagnesemia, hyperkalemia, hypernatremia, hypermagnesemia, decreased sulfate
– Malnutrition: high-transport protein losses, amino acid abnormalities
– Uncontrolled diabetes mellitus / advanced glycosylation end products (AGE)
– Growth retardation
– Hormonal abnormalities
– Obesity

7. Neurologic / Psychiatric
– Cerebral metabolic abnormalities
– Psychological abnormalities: depression, noncompliance, cognitive dysfunction
– Multiple neuropathies: rapidly evolving polyneuropathy, ischemic optic atrophy, chronic inflammatory demyelinating polyneuropathy, diabetic/uremic neuropathy
– Restless legs, nocturnal myoclonus
– Autonomic neuropathy
– Cerebral vascular disease: multi-infarct, dementia, embolic stroke
– Altered quality of life: job-related stress, disrupted work function

Table 1. continued

8. Gastrointestinal
– Pancreatitis
– Motility abnormalities: gastroparesis, reflux, bloating
– Gastroesophageal reflux/bloating
– Nonobstructive mesenteric infarction (NOMI)
– Ascites: standard, chylous
– Gastrointestinal bleeding
– Hepatic complications: steatonecrosis, hepatitis C, hepatitis B, hepatitis G, liver abscess
– Esophagitis: infectious, inflammatory
– Ischemic/necrotizing colitis
– Esophageal rupture
– Drug toxicity: cisapride

9. Dermatologic / Other
– Pruritus
– Calciphylaxis
– Contact/hypersensitivity dermatitis
– Drug toxicity

10. Hematology / Oncology
– Anemia / red blood cell metabolism: infection/rHu-EPO response, angiotensin converting enzyme (ACE)
  inhibitors
– Abnormal platelet morphology and function
– Coagulation abnormalities: hypercoagulability, fibrinolysis
– Bleeding diuresis
– Neoplasia: renal cystic disease, urologic tumors, peritoneal

11. Transplant / Immune
– Graft rejection
– Post-transplant infection: pancreatitis, PD catheter
– Renal allograft thrombosis
– Post transplant ascites
– Immune defects: systemic, intraperitoneal
– Hypogammaglobulinemia
– Dialysate-induced immune defects
– Systemic lupus erythematosus (SLE) reactivation

12. Hospitalization risk/complication
– Increased hospitalization
– Modality mortality effect
– Special populations at risk: HIV, elderly, diabetic, high-transport patients
– Postoperative complications:
  – malnutrition (enteral feeding, gastrostomy, jejunostomy)
  – uncontrolled hyperglycemia
  – inadequate solute clearance
  – postoperative wound infection (amputation, revascularization, cardiac, aorto-femoral)
  – respiratory failure (re-intubation)

Technique-specific (Noninfectious) Complications

Peritoneal Membrane Failure

Long-term alterations in the peritoneal membrane are most likely related to the continuous exposure of the membrane to dialysate solutions containing glucose, low pH, and lactate. Little data are available on long-term PD membranes, resulting in discrepancies in the literature on membrane transport characteristic changes. A number of reports have suggested that creatinine mass transfer coefficient (MTC) significantly increases and ultrafiltration (UF) capacity decreases after 4 years on PD, with little effect on the urea MTC. Since the peritoneal equilibration test (PET) results usually mirror MTC results, the same findings would be expected in populations evaluated with PET. The increased transport characteristics suggest an increase in the effective peritoneal surface area and/or permeability due to diminished interstitial resistance over time. A 7-year follow-up study of patients on PD reported 23 patients who demonstrated increasing creatinine MTC and/or dialysate/plasma (D/P) creatinine after the third year [29]. Peritoneal rest for 4 – 12 weeks helped stabilize changes in MTC. Therefore, early recognition of transport alterations and peritoneal resting may allow a patient to continue on PD for longer periods of time. In a group of 90 patients with peritoneal membrane data tracked over 5 – 17 years, the creatinine MTC significantly increased over time concomitant with a decrease in UF capacity [97]. Urea MTC remained unaltered. Eighty percent of PD patients maintained stable solute transport characteristics, while 27% demonstrated an increase in back diffusion of solute and an increase in UF failure. Children may also develop membrane failure, especially after infection with Group A streptococcus.

Glucose dialysate modulates the function of mesothelial cells and peritoneal fibroblasts. In vitro exposure of peritoneal membrane cell lines can decrease proliferation rate, increase expression of profibrotic cytokine-transforming growth factor (TGF-β), metalloproteinases, advanced glycosylation end products, and fibronectin. Newer solutions (e.g. amino acid, icodextran, bicarbonate) may potentially "rescue" the peritoneal membrane from the fibrosis triggered by the above substances. An increase in transforming growth factor-β (TGF-β1), and an increase in collagen fibers with the generation of smooth muscle cells in the media may also play a role. Icodextran may extend PD usefulness by optimizing UF based on its molecular size. No effect was observed on permeability, but there was an increase in convective flow through the small pore system. UF failure due to a large effective peritoneal surface area may respond to icodextran. An alternative treatment option involves changing a patient to automated PD with short cycles.

A number of markers of peritoneal mesothelial cell function have been examined in an attempt to predict patients at risk for decreased membrane function over time. The dialysate effluent can provide valuable indirect information on the stability of the peritoneal membrane [42]. Cancer antigen 125 (CA^{125}), phospholipid and hyaluronic acid are produced by mesothelial cells, and CA^{125} levels reflect mesothelial cell mass or turnover. Although CA^{125} may not necessarily correlate with the actual number of mesothelial cells in the PD effluent, a decrease in CA^{125} in an individual patient reflects a decrease in overall mesothelial mass. In an attempt to preserve

Table 2. Approach to Ultrafiltration Failure*

History:	Onset, time on peritoneal dialysis, shortness of breath, weight gain, residual renal failure, drain pattern
Exam:	Location of edema: distal/central, pleural effusion, scrotal edema
Membrane characteristics:	Stable, increased, decreased
Diagnostic tests:	Serum albumin, plain radiographic exam (chest, abdomen), CT scan, CT with intraperitoneal contrast, radiolabeled scintigraphy
Treatment:	Peritoneal rest, surgical repair, cycler (APD), transfer to HD, phosphatidylcholine, heparin, alternate dialysate solutions†

*Ultrafiltration risk factors: time on PD, percent of dialysate glucose absorption, peritonitis rate, hyperosmotic dialysate frequency, impaired transcellular water transport, acetate dialysate, high intraperitoneal pressure.
† Short chain polypeptides, glucose polymer, amino acid, ultra-low sodium dialysate solutions.

the peritoneal membrane and avoid peritonitis, it may be important to avoid excess 4.25 g/dL dextrose, match modality with membrane transport, and avoid uncontrolled blood sugars or high glycosylated hemoglobin (HbA_1C > 8) [94]. The data are less clear regarding the optimal effective membrane resting period; the value of using intermittent vs. continuous PD; and the use of small-dose heparin surfactants, ADCON-D, mesothelial cell implantation, or addition of vitamin E or phosphatidylcholine to the dialysate.

Ultrafiltration (UF) Failure

UF failure can be classified as a true or an apparent loss of UF. The true loss refers more to specific membrane transport alterations, anatomical abnormalities, increase in lymphatic absorption, or catheter dysfunction. Apparent loss implies medical noncompliance, a mismatch between the transport characteristics and the prescription, loss from residual renal function or prescription noncompliance.

UF failure occurs in 6.2 – 11% of patients, and appears to increase with time spent on PD. After 6 years on PD, approximately 30% of patients may develop UF failure [57]. The approach to UF failure should consist of a clinical history, physical examination, characterization of membrane transport category, and an analysis of serum albumin (Table 2). Additional studies may include: plain X-ray of the chest and abdomen, computed tomography (CT) with or without intraperitoneal (IP) contrast, and radiolabelled scintigraphy. Typically, the net UF is > 400 mL in 4 hours using a 4.25% glucose dialysate (3.86%) solution.

UF failure can be categorized according to PET results (Table 3). Patients presenting with stable PET results may have catheter malposition, subcutaneous dialysate leak, or leak into the scrotal area with significant genital edema. Other etiologies for UF failure with stable PET test results include increased lymphatic absorption, increased intra-abdominal pressure and impaired transcellular water transport. While UF failure in PD is most likely not due to an increase in IP pressure,

Table 3. Usefulness of PET for Diagnosis of Ultrafiltration Failure in PD*+

PET Results (solute transport rate)	Possible diagnosis	Diagnostic Tests	Treatment
Increased (high)	Type I membrane failure	% glucose absorption	Short dwell times Peritoneal resting: 1 month ? alternate dialysate solution Avoid hyperosmotic dialysates (if possible)
	Peritonitis	Dialysate cultures	Aggressively treat peritonitis (antibiotic, heparin)
Stable (average)	Catheter malposition	X-ray	Surgical (laparoscopic, thoracoscopy, laparotomy)
	Dialysate leaks	CT with contrast scintigraphy technetium 99^{m} albumin	Surgical Alter dialyzing position
	Increased lymphatic reabsorption	Dextran, albumin+, exclusion	? phosphatidylcholine IP Transfer to HD
	Increased intra-abdominal pressure	IP pressure transducer ? rectal pressure monitor	Decrease volume
	Impaired transcellular water transport	D/P sodium (2 hours) UF with 1.5% vs. 4.25% glucose	Short dwell times Decrease % glucose ? transfer to HD
Decrease (low)	Type II membrane failure (sclerosing peritonitis)	Surgical exploration Peritoneal biopsy	Hemodialysis Catheter removal Prednisone /Imuran Tamoxifen ADCON
	Adhesions	Scintigraphy	Laparoscopic laser lysis ? tidal PD

* UFF in PD is defined as edema, inability to achieve dry weight with hypertonic exchanges (< 200 cc UF with 4.25% dilaysate). + Possible risk factors: time on PD,% dialysate glucose absorption, peritonitis rate, hyperosmotic dialysate frequency, impaired transcellular water transport, acetate dialysate, chronically high intraperitoneal pressure.

high IP pressures can decrease overall UF rates. For each 1 cm increase in water, there is a 70 mL decrease in UF after 2 hours. Patients with increased or high PET results may benefit from peritoneal resting or the use of alternate solutions, e.g. glucose polymer. Sclerosing peritonitis and adhesions should be considered as etiologies for a decreased or low PET result. Peritoneal resting is beneficial in these patients with peritoneal UF failure.

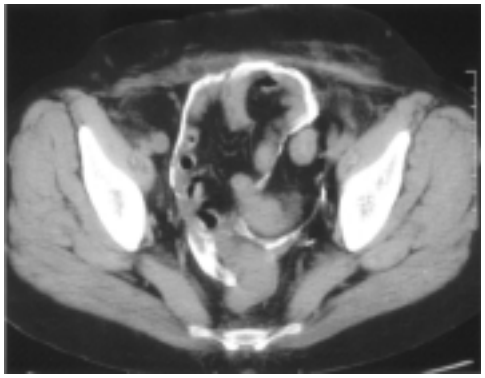


Figure 1a.

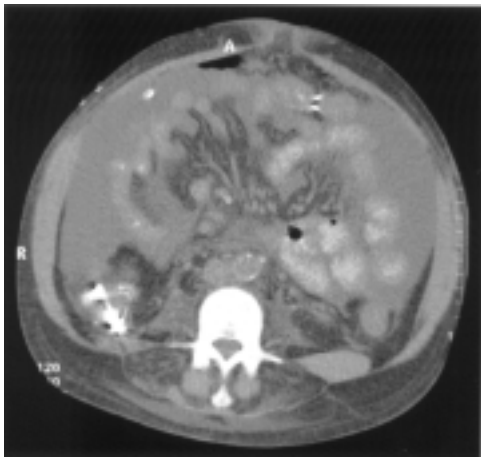


Figure 1b.

Figure 1. a: CT scan demonstrating a calcified peritoneum with centrally adherent bowel loops which conglomerate and lose the normal intestinal loop pattern (Courtesy, Burkhart, J.).
The normal intestinal distribution appearance is noted in Figure 1b.

Sclerosing Encapsulating Peritonitis (SEP)

A number of reports have described the development of SEP in continuous ambulatory peritoneal dialysis (CAPD) patients. The annual incidence rate is approximately 0.37/1000 patient-years. This rate may vary by country with 0.9 – 1.7% incidence in Japan, 0.7% occurrence in Australia, and 0.54% in Canada. While SEP is a rare complication, it is nonetheless serious and, in some cases, life-threatening. Depending on the study reported, there can be a predominance of either men or women with an increased occurrence after age 40 and after 4 years of PD [116].

For patients on PD more than 4 years presenting with abdominal pain, decreased UF capacity, progressive malnutrition (decreased weight), decreased serum albumin, anorexia, and blood stained effluent, SEP should be considered. The diagnosis can be made on the basis of a plain abdominal X-ray indicating obstruction, dilated small bowel loops, calcified peritoneum (Figure 1); abdominal ultrasound findings of matted bowel loops, an echogenic "sandwich" appearance around bowel loops with loculating ascites; CT indicating dilated bowel loops, loculated ascites, dense thickening of the peritoneal membrane, centrally adherent bowel loops which conglomerate with loss of normal intestinal loop pattern and luminal narrowing; or laparoscopy with peritoneal biopsy demonstrating inflammatory intra-abdominal infiltrates, dilated lymphatics, fibrotic thickening of the peritoneal membrane, and an absence of the mesothelial cell layer.

The multiple postulated etiologies for SEP include recurrent severe peritonitis, CAPD duration > 4 years, dialysate composition (acetate, hyperosmotic glucose, low pH), multiple abdominal surgeries, various drugs (β-blockers, disinfectants, IP antibiotics), and catheter foreign body. Mortality from SEP varies from 20 – 93%. A fatal outcome can occur in a significant percent of patients due to bowel obstruction, or complications from surgery and malnutrition. When surgery is employed for diagnosis or adhesion relief, special attention should be given to avoiding infection, optimizing nutrition with early total parenteral nutrition (TPN) and aggressive hemodialysis (HD) treatment.

Conservative treatment involves the removal of the PD catheter, transfer to HD and initiation of TPN to rest the bowel. Prednisone 30 – 50 mg/day and/or azathioprine 100 mg/day may help with overall patient outcome. Tamoxifen 20 mg every 12 hours orally (PO) for 6 – 12 months may decrease peritoneal membrane fibrosis in some patients. Newer substances to decrease adhesion formation (ADCON-D) may theoretically be helpful at the time of surgery. Transplantation may play a role in optimizing long-term outcomes.

Because most patients do not develop the risk for SEP until after a period of time on PD, screening tests may be useful in identifying individuals at increased risk for SEP. Changes in the morphology of the mesothelial cell appearance, abnormal peritoneal membrane function tests and typical findings on radiographic survey (e.g. CT scan, ultrasound) may be helpful.

Catheter-related Complications

A number of complications may be associated with the insertion of a PD catheter. Falcon et al.'s report indicated 27.6% of catheters develop a complication [33]. The complications include malposition (13%), dialysate leak (8.9%), hemoperitoneum (3.6%), peritonitis (1%), surgical wound infection (0.5%), and chylous ascites (0.5%). Recognizing risk factors and designing strategies to prevent leaks decreases the incidence of PD leak. Risk factors for these complications following insertion are previous abdominal surgery, particularly if it affected the peritoneal membrane; and early use of the catheter (< 5 days after implantation).

Catheter-related complications can result in catheter loss. The major causes for catheter loss are infection (80%), catheter defect (5%), PD failure (5%), drain failure (4%), and leak (3%). Overall catheter survival at one year is approximately 80%, decreasing to 50% by 3 years. The placement site, surgical technique, and use of perioperative antibiotics all play a role in avoiding early postoperative catheter-related complications. A paramedian incision is associated with the least complications. Furthermore, lower risk is observed when the catheter is fixed to the lower peritoneum with an additional suture. Several reports have delineated the benefit of inserting the peritoneal catheter 3 cm lateral to the linea alba, with placement of one purse-string suture fixed to the peritoneal membrane along the inner cuff, a second fixed on the dorsal fascia of the rectus muscle around the outer side of the cuff, and a third suture around the catheter in the ventral fascia [102]. Studies have not demonstrated a significant difference between bedside and standard surgical placement.

Standardizing laparoscopic placement may be helpful in improving long-term catheter survival. Centers may use a closed Verres needle technique or an open Hassan technique for the initial abdominal CO_2 gas insufflation. The smallest number of 3–5-mm ports should be made and 10- to 12-mm access ports should

be avoided. Ideally tight 2-layer closure should be performed. The post-laparoscopic leakage and herniation rates are dependent on access port placement position (lower abdominal quadrant), the number of ports, size (10-mm vs. 5-mm), closure (partial vs. full thickness), and time delay until the institution of PD. Fewer problems are observed with full fascial wound closure including the peritoneum.

A number of different catheters have been designed to optimize long-term catheter survival. These include the Oreopolus-Zellerman, Swan neck, Cruz catheter, Montcrief-Popovic catheter, and the Tenckoff single and double cuff catheters. Obese patients with a body mass index (BMI) > 40 kg/m^2 may benefit from using a presternal PD catheter consisting of 2 silicone rubber tubes formed by a titanium connector. Two-year catheter survival approximates 88%. The role of catheter configuration in the subsequent development of mechanical or infectious complications is unclear. Several reports comparing catheters with either single or double cuffs have demonstrated no significant differences in catheter survival, episodes of peritonitis, and exit site infection. Patients with the Swan neck catheters have a lower incidence of cuff extrusion and pericatheter leakage with better catheter survival, although the incidence of exit site tunnel infections and migrations is no better than with the standard Tenckoff catheter in some studies.

Peritoneal catheter dysfunction is a common complication of PD and a frequent source of morbidity, catheter loss, and additional cost of therapy. Inadequate flow occurs in 6 – 55% of catheters. Specific causes for catheter malfunction include intraluminal obstruction from blood, omentum, or fibrin; extraluminal obstruction from omentum, adhesions, catheter kinks, and constipation; and catheter migration with or without obstruction (Figure 2). Extraluminal obstruction and migration can result in one-way obstruction with slow infusion or drainage and abdominal pain with infusion or drainage. Catheter position may be assessed by a flat plate of the abdomen or CT peritoneography. Enemas, physical activity, higher dialysate inflow pressures, and catheter manipulation with a semiflexible wire under fluoroscopy may be helpful. Additional reported approaches include manipulation with a Fogarty catheter, laparoscopic re-positioning or open surgical exploration with omentectomy and pelvic suture tacking. In the setting of fibrin or a clot, it may be helpful to use urokinase or streptokinase 10,000 units in 2 mL injected into the catheter for 2 hours. Heparin 500 – 2000 units/L added to the dialysate may also provide some assistance. Preservation of the external tract in a dysfunctional catheter decreases time to catheter usage; otherwise, the catheter should be replaced.

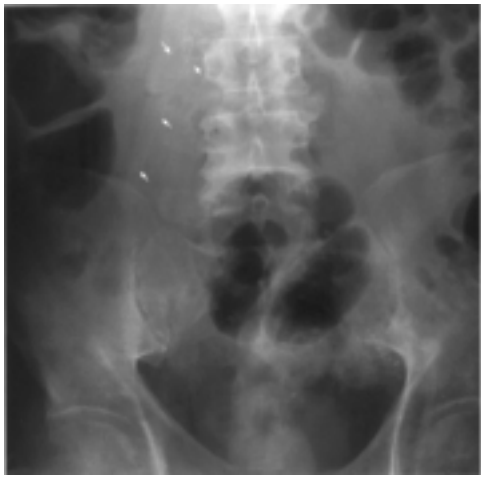


Figure 2. The arrows designate a peritoneal dialysis catheter which has migrated out of the pelvis and resulted in inadequate dialysis drain volumes (apparent ultrafiltration failure).

Both hernias and dialysate leaks may develop in patients following the placement of a PD catheter [7]. Several different types of

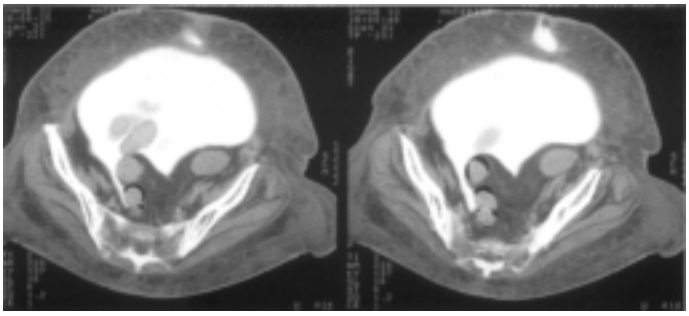


Figure 3. Computed tomographic peritonography delineates a subcutaneous pericatheter leak in a patient with ultrafiltration failure.

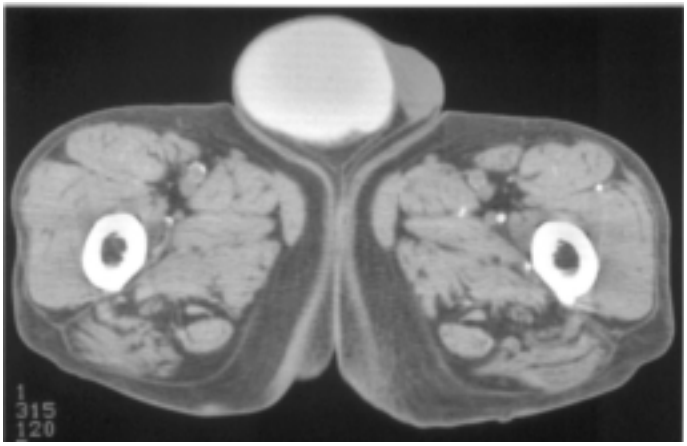


Figure 4. Scrotal edema in this male CAPD patient is characterized by the presence of contrast in the scrotal area which was secondary to a patent foramen vaginalis as seen on computed tomographic peritonography.

hernias may develop including internal cuff, umbilical, inguinal and/or incisional. A significantly greater incidence of hernia (inguinal, incisional, and umbilical) occur in autosomal dominant polycystic disease (ADPKD) patients on PD. Increased exchange volumes of 2.5 – 3 L is not associated with a significantly increased risk for hernia formation. The cycler is, however, associated with a decreased risk of hernia development due to the supine position for treatment.

All abdominal wall hernias should be repaired before PD is initiated to prevent progressive worsening. Consider 2 – 4 weeks of HD after hernia repair to minimize recurrence risks. If HD is not feasible, use supine intermittent low-volume dialysis for 2 – 4 weeks.

Dialysate leakage may occur at the exit site, in subcutaneous tissue (Figure 3), scrotum (Figure 4), labia, or pleural peritoneal (hydrothorax). The most common causes for scrotal edema are hernias and leaks along the catheter, or fluid overload. Catheter infection and peritonitis followed by a leak often lead to catheter loss and probably indicate an infection of the catheter's deep cuff. Infections developing following a leak usually resolve. Radionucleotide scanning, peritoneal scintigraphy with Tc^{99} M-colloid, and ultrasound may be helpful in identifying the site of leakage. Localization of leaks and abnormal IP collections by CT peritoneography are helpful if surgical management is contemplated. For early leakage, the treatment options include dialysis in the supine position with low volumes for 3 – 5 treatments, or transfer to HD for 1 – 2 weeks while withholding PD. A larger leak volume, malnutrition, and pa-

tient age > 80 correlate with a greater need for surgical repair.

Laparoscopic revision of a previous malfunctioning catheter may be complicated by dialysate leakage through the laparoscopic entry port. Restoration of an intact surface and an open defect in the peritoneum usually need 5 – 8 days of healing time, independent of the initial size of the defect. Increases in intra-abdominal pressure may delay abdominal wound healing by decreasing rectal sheath blood flow, resulting in tissue hypoxia. The early initiation of PD with 2-L volumes may contribute to this problem. Dialysate leak and hemoperitoneum have been observed after laparoscopic cholecystectomy in CAPD patients. Radionucleotide scanning, peritoneal scintigraphy with Tc^{99} M-colloid and ultrasound may be helpful in identifying the site of leakage.

Other reported catheter-related complications include omental herniation, pneumoperitoneum, erosion of the catheter into the mesenteric vessels, small bowel obstruction, and organ perforation: gall bladder, small bowel, large intestine, or bladder.

Hemoperitoneum

Hemoperitoneum (blood in the dialysate) may result from a large number of etiologies including: catheter-related splenic infarction, perforation of the gall bladder, amyloid bowel with perforation, exogastric leiomyosarcoma, hepatic angioleiomyoma, rupture of polycystic liver, rupture of hepatic tumor, ilioleiomyoma, carcinomatous liver, pericardiocentesis, retroperitoneal hematoma, menses, ruptured hemorrhagic ovarian cyst, giant multicystic hemangioma, perforated diverticulae and ischemic colitis. Wang et al. have characterized hemoperitoneum into 3 distinct groups [112]. Group I refers to benign retrograde bleeding from fallopian tubes, ovulation, catheter repositioning, femoral hematoma, immune thrombocytopenia purpura (ITP), warfarin, peritoneal entry after transplant, strenuous exercise, ectopic endometriosis, and use of hypertonic dialysate. Group II includes IP bleeding with significant pathology, usually persisting for > 36 hours, and characterized by a decrease in hematocrit (HCT) and blood pressure. Group II individuals may warrant laparotomy. Etiologies include pancreatitis, polycystic kidney disease with intracyst bleeding, postoperative bleeding and renal angiomyolipoma. Group III refers to significant bleeding requiring specified interventions. The etiologies include peritoneal laceration, ovarian cyst rupture, ruptured spleen or splenic artery, pseudoaneurysm, bowel perforation, or abdominal aortic aneurysm rupture.

Dialysis-related Pain Syndrome

Abdominal pain not related to infection may occur in the setting of PD. Once peritonitis is excluded, other etiologies should be considered including pancreatitis; cholecystitis; perforated ulcer or small bowel; ruptured diverticuli; incarcerated omentum; small bowel hernia; appendicitis; diverticulitis; mesenteric insufficiency; ischemic colitis; bowel infarction; and catheter erosion into vagina, bladder, or bowel. Patients on dialysis can develop a surgical abdomen independent of true peritonitis. Patients with persistent localized abdominal rebound, dilated loops of bowel, increased intra-abdominal air with pain, with multiorgan peritonitis or refractory peritonitis warrant consideration for surgical exploration. Dialysate infusion pain may result from conventional (40 mM) lactate dialysate. Bicarbonate and bicarbonate/lactate solution may decrease infusion pain. Rectal

pain with infusion may be related to the catheter being directed towards the posterior pelvis. If the pain does not resolve, the catheter may need manipulation or revision.

Infections

Overview of Peritonitis

Infectious complications represent the most important reason for patient drop-out from PD programs. The major sources of infection can be characterized into peritonitis and catheter exit site infection (CESI). As outlined in Table 4, gram-positive organisms (typically Staphylococcus species) are the most common cause of peritonitis and CESI, with gram-negative bacterial and fungal infections accounting for a lesser percentage. A wide variety of pathogens has been reported. Infections can occur via a number of different routes including intraluminal (touch contamination), periluminal (catheter tracking), transmucosal (via the intestinal wall, especially with acute constipation treatment and/or diarrhea), hematogenous, intra-abdominal, or via other loci (i.e. pulmonary, gynecologic, or urinary). The rate of sterile peritonitis may be as high as 20% depending on the culture technique (delayed culture inoculation, insufficient sample, initiation of treatment prior to culture, and atypical pathogens). Initial no growth peritonitis accounted for 14% of the episodes of peritonitis in the Network 9 Peritonitis and Catheter Survival study. Thirteen of 37 (35%) patients were positive with re-culturing (3 fungus, 5 gram-negative, 5 gram-positive) [13]. There was a greater percentage of patients over age 70 with gram-positive organisms, and patients who develop sterile peritonitis and place additives in their dialysate. Newer dialysis systems have decreased peritonitis risk. Optimizing dialysate sampling for culture is essential to the accurate diagnosis of peritonitis. Several traditional culture approaches are: standard culture of small amounts of dialysate; culturing large amounts with centrifugation, filtration, and removal of any antibiotics which may be present in the dialysate; a blood culture technique depending on lysis of leukocytes to increase the yield; and BACTEC, a radioactive culture technique.

Mycobacteria may be difficult to culture in certain settings. Patients with human immunodeficiency virus (HIV), hepatitis B (HBV), or active cytomegalovirus (CMV) infections, uncontrolled DM, or malnutrition are at increased risk for infection. A large number of case reports (Table 4) in the literature have delineated the broad spectrum of organisms (gram-negative and gram-positive bacteria, fungi, molds, parasites, and mycobacteria) responsible for infections in PD. *Penicillosis marneffei*, a newly emerging disseminated and progressive mycosis, will likely be seen increasingly in PD peritonitis in the future. There are significant differences in the course and treatment success depending on the type of organism.

Peritonitis

The diagnosis of peritonitis depends on the presence of abdominal pain and visibly cloudy fluid. Rarely, patients may present with abdominal pain out of proportion to the white blood cell (WBC) count, raising concerns for atypical mycobacteria, enterococci, fungus, or a more unusual organism. The total number of dialysate WBCs is usually > 100 cells/μL. The WBC differential may offer a

Table 4. Infection Complications by Organism

Organism	**Peritonitis**	% cases
Gram-positive[1]		50 – 75%
Staphylococcus aureus[2]	(40-50%)	
Staphylococcus epidermidis[2]	(40-60%)	
Streptococcal species	(3-15%)	
Enterococci	(3-10%)	
Gram-negative[3]		15 – 25%
Pseudomonas[4]	(5-10%)	
Non-*Xanthomonas*[4]	(10-15%)	
Fungus[5]		< 2%
Candida albicans	(75-80%)	
Non *C. albicans*	(20-25%)	
Other[6]		< 2%
Sterile		10 – 20%
Organism	**Catheter Exit Site**	% cases
Gram-positive		70 – 75%
S. aureus	(40-50%)	
S. epidermidis	(50-60%)	
Gram-negative		12 – 20%
Pseudomonas	(60-55%)	
Eschericae coli	(40-35%)	
Fungus		5%
C. albicans	(80-85%)	
Other	(15-20%)	

[1]Case reports: Rhodococcus equi, Bacillus cereus, Neisseria monocytogenes, Streptococcus pyogenes, Clostridium difficile, Nocardia asteroides. [2]Percent methcillin-resistant *S. aureus* and S. epidermidis are center dependent. [3]Case reports: Xanthomonas maltophilia, Agrobacterium radiobacter, Neisseria meningitidis, Capnocytophaga species, Moraxella (Branhamella) catarrhalis, Oligella urethralis, Pasteurella multocida, Acinetobacter, Neisseria cinerea, Aeromonas hydrophila, Flavobacterium, Alcaligenes xylosoxidans, CDC group EO-3, Neisseria sicca. [4]Escherichia coli, Klebsiella species, Acinetobacter, Enterobacter, Seuabia. [5]Case reports: Cryptococcus, Rhodotorula rubra, Aurobasidium pullulans, Histoplasma capsulatum, Trichosporon inkin. [6]*Parasites:* Giardia lamblia, Anisabis larva. *Mold:* Pennicillium species, Verticillium species, Aspergillus species, Biipolaris hawaiiensis, Exophiala jeanselomei, Fusarium species, Paccilomyces ravotii, Curvularia lunata (black mold), Aspergillus niger, Trichoderma gibrachiatum. *Mycobacterium:* tuberculosis, atypical mycobacteria (fortuitum, kansasii, gordonae, phlei)

Table 5. Empiric Therapy[1]

Treatment	Loading	Continuous Dose[1] (dose in each exchange)	Intermittent Dose[2] Administer in 1 exchange q day (dwell 4-6 hours) Residual Renal Function (cc/day) Anuria (< 500)	Non-anuria (> 550)
Cefazolin	500 mg/L	125 mg/L	500 mg/L	Increase dose by
Cephalothin	500 mg/L	125 mg/L	(15 mg/kg)	25%
Ceftazidime	250 mg/L	125 mg/L	1000 mg	1000 mg
Cefipime[6]	500 mg/L	125 mg/L	250 mg/L IP BID	
Gentamicin[3]	8 mg/L	4 mg/L	0.6 mg/kg body weight	0.6 mg/kg; IV/IP initial dose[7]
Tobramycin			See footnote for maintenance dose recommendations	
Vancomycin[4]	1000 mg/L (IP)	See footnote for maintenance dose recommendations[5]		
Aztreonam	1000 mg/L	250 mg/L	1000 mg/day	

Potential antibiotic regimens include: vancomycin + aminoglycoside, aztreonam or ceftazidime, cephalosporin + aminoglycoside, or cefipime

[1]Medications can be given IV or IP. Dosages are recommended for 1.73 m^2. [For patients with an increased risk for ototoxicity, use aminoglycoside alternative (aztreonam) plus vancomycin or cefipime alone.] Gentamicin plus cephalosporin can be given in the same exchange, dwell time 4 – 6 hours.

[2]Dose per drug level (dwell 4 – 6 hours). Due to decreased post antibiotic effect, once-daily dosing for cephalosporins may result in sub-optimal results.

[3]IV = 1.5 mg/kg; check level at 48 hours; redose intraperitoneally when level <2 mcg/L (Accurately document level prior to next dose as recommended)

[4]Check random level at 72 hours, redose when < 18 μg/L. For patients with RRF consider redosing in 3 – 5 days vs. 5 – 7 days in anuria.

[5]Indications for continued vancomycin dosing: PCN allergic, shock, methicillin resistant, not responding to standard treatment (check random level at 72 hours, redose when < 18 mg/ml)

[6]Use for broad spectrum coverage of gram-negative in place of ceftazidime and aminoglycoside.

[7]If administering with vancomycin, give vancomycin IP and aminoglycoside IV.

clue to the specific type of infection, with polymorphonuclear leukocytes (PMNs) being more common in bacterial peritonitis, while monocytes (> 10%) occur in fungal peritonitis, and increased lymphocytes may indicate an atypical infection such as mycobacterium. The presence of eosiniphils (> 100/μL) may indicate the usually benign con-

Table 6. Peritonitis Treatment Guidelines

Introduction

A. Reasons for re-assessing treatment
1. Increased number of vancomycin-resistant enterococci (VRE) in dialysis
2. Increased risk for VRE peritonitis
3. Risk of inadequate treatment regimens for peritonitis
4. Peritonitis related drop out patterns
5. Postantibiotic effect (PAE) vancomycin vs. intermittent cephalosporin
6. Hospitalization risk (> 50%)

B. Model protocols after Recommendations of the Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis 1996

C. Complete organism treatment sheet on all patients

D. Define benchmark peritonitis rate

Adapted from Keane et al.: Perit Dial Int, 1996, 16; 11.

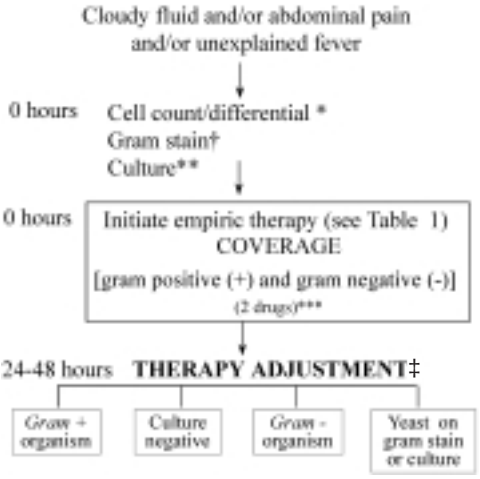


Figure 5. Initial Clinical Presentation with Peritonitis.
*Cell count > 100 cells/HPF (high power field) > 50% neutrophils suggest bacteria, > 10% monocytes suggest fungal, and lymphocytosis may indicate tuberculosis. †For a positive gram stain; intracellular organisms warrant rifampin if no contraindications exist. If yeast on gram stain, initiate antifungal treatment and await culture prior to removing catheter, unless patient's condition is deteriorating. **Culture technique (see text). ‡Check culture, verify sensitivity, adjust antibiotics (see text). ***Piperacillin or cefipime may replace ceftazidime in certain medical centers.

dition of eosinophilic peritonitis, although a fungal infection should also be considered. Eosinophilic peritonitis usually responds spontaneously, but low-dose prednisone has been used in persistent cases, with variable response.

A gram stain is positive only in approximately 20% of cases with peritonitis. Empiric treatment is usually begun after cultures are obtained. Figure 5 summarizes empiric therapy and subsequent adjustment after culture results are known, typically 24 – 48 hours. Both gram-positive and gram-negative organisms should initially be covered unless the infection represents a documented relapse. Patients who require continued vancomycin

Table 7. Dosages for Some of the More Frequently Used Antibiotics

Drug	Dosing	
	Intermittent (1 dose/day unless otherwise specified)	Continuous (mg/L unless otherwise specified)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD12
Gentamicin[1]	0.6 mg/kg	LD 8, MD 4
Netilmicin	0.6 mg/kg	LD 8, MD 4
Tobramycin[1]	0.6 mg/kg	LD 8, MD 4
Cephalosporins[2]		
Cefazolin	15 mg/kg	LD 500, MD 125
Cephalothin	15 mg/kg	LD 500, MD 125
Cephradine	15 mg/kg	LD 500, MD 125
Cephalexin	500 mg PO QID	NA
Cefamandole	1000 mg	LD 500, MD 250
Cefepime	250 mg BID	LD 500, MD 250 (BID)
Cefmenoxime	1000 mg	LD 100, MD 50
Cefoxitin	ND	LD 200, MD 100
Cefuroxime	400 mg PO or IV	LD 200, MD 100-200
Cefixime	400 mg PO	NA
Cefoperazone	ND	LD 500, MD 250
Cefotaxime	2000 mg	LD 500, MD 250
Cefsulodin	500 mg	LD 50, MD 25
Ceftazidime	1000 mg	LD 250, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Ceftriaxone	1000 mg	LD 250, MD 125
Penicillins		
Azlocillin	ND	LD 500, MD 250
Mezlocillin	3000 mg IV BID	LD 3000 mg IV, MD 250
Piperacillin	4000 mg IV BID	LD 4000 mg IV, MD 250
Ticarcillin	2000 mg IV BID	LD 1000-2000 mg IV, MD 125
Ampicillin	ND	MD 125; or 250-500 mg po BID, 250-500 mg po QID.
Dicloxacillin	ND	MD 125
Oxacillin	ND	MD 125
Nafcillin	ND	250-500 mg PO every 12 hours
Amoxacillin	ND	
Quinolones		
Ciprofloxacin	500 mg PO BID	Not recommended
Fleroxacin	800 mg PO loading, then 400 mg PO daily	Not recommended
Ofloxacin	400 mg PO loading, then 200 mg PO daily	Not recommended
Others		
Vancomycin	15 – 30 mg/kg for 5 – 7 days	LD 1000, MD 25
Teicoplanin	400 mg IP BID	LD 400, MD 40[a]
Aztreonam[3]	1000 mg	LD 1000, MD 250

Table 7. continued

Drug	Dosing	
	Intermittent (1 dose/day unless otherwise specified)	Continuous (mg/L unless otherwise specified)
Clindamycin	ND	LD 300, MD 150
Erythromycin	500 mg PO QID	LD ND, MD 150
Metronidazole	500 mg PO/IV TID	ND
Minocycline	100 mg PO BID	NA
Rifampin	450-600 mg PO daily or 150 mg IP TID-QID.	NA
Antifungals		
Amphotericin	NA	1.5
Flucytosine	1000 mg daily PO or 100 mg/L IP each exch x 3 days, then 50 mg/L/exch 200-8000 mg PO	50
Fluconazole	ND	ND
Ketoconazole		NA
Miconazole		LD 200, MD 100-200
Combinations		
Ampicillin/sulbactam	2000 mg every 12 hours	LD 1000, MD 100
Imipenem/ciliastatin	1000 mg BID	LD 500, MD 200
Piperacillin/tazobactam[4]		
Trimethoprim/sulfamethoxazole[5]	320/1600 mg q. 1 – 2 days PO	LD 320/1600, MD 80/400

The route of administration is intraperitoneal (IP) unless otherwise specified. The pharmacokinetic data and proposed dosage regimens presented here are based on published literature reviewed through January 1996. There is no evidence that mixing different antibiotics in dialysis fluid (except for aminoglycosides and penicillins) is deleterious for the drugs or patients. Do not use the same syringe to mix antibiotics.
[a]This is in each bag x 7 days, then in 2 bags/day x 7 days, and then in 1 bag/day x 7 days.
LD = loading dose; MD = maintenance dose; NA = not applicable; ND = no data; IV = intravenous; IP = intraperitoneal; PO = oral; BID = twice a day; TID = three times a day; QID = four times a day

NOTE: CAPD patients with residual renal function may require increased doses or more frequent dosing, especially when using intermittent regimens.
[1]Levels should be obtained to guide dosing interval. Consider redosing when level falls < 2 μg/L
[2]Concerns exist regarding lack of post-antibiotic effect
[3]Can be utilized for penicillin-allergic patients
[4]Zosyn (piperacillin/tazobactam) replaces timentin for serious polymicrobial nosocomial infections. Adapted from Keane et al. Perit Dial Int 1996;16:561
[5]Stenotrophomonas is uniquely sensitive to trimethoprim/sulfamethoxazole

need drug level determinations to maintain a serum level of > 18 μg/mL, especially in patients with residual renal function. Trough vancomycin levels may predict the risk for relapse of gram-positive infections. A low 4-week main trough (< 12 μg/mL) or initial 7-day trough (< 14 μg/mL) vancomycin level indicates an increased risk for subsequent peritonitis relapse. Dosing intervals of approximately every 5 days (patients without residual renal function) and 3 – 4 days (residual renal function patients) are needed to achieve therapeutic levels. Table 7 lists dosages for commonly used antibiotics. A new class of antibiotics, the oxazolidinones, may offer increased effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA).

Even though *Staphylococcus epidermidis* is the most common touch contamination pathogen, the frequency of infection from more virulent S. aureus has increased dramatically in some centers. Patients with nasal carriage of *S. aureus* are at increased risk (4 – 6.7 times that of non-carriers) for the development of *S. aureus* CESI and/or peritonitis. While patients with gram-negative peritonitis respond to appropriate antibiotic treatment, pseudomonal infections, especially CESI, are difficult to cure. Early and aggressive therapy is essential because of significant morbidity. Prevention, including disinfecting showers and soaking shower heads with sodium hypochlorite, and disinfecting areas with stagnant water, is the key to decreasing the incidence of outbreaks.

Maneuvers which alter bowel mucosa and/or cause diarrhea increase the risk for gram-negative infection. These include enemas, frequent suppositories, alternating constipation/diarrhea, diabetic colon dysfunction, *Clostridia difficile* diarrhea and H_2 blockers. The majority of fungal infections are due to *Candida* species usually after antibiotic treatment, malnutrition, or with additional risk factors (e.g. DM with esophagitis). Percutaneous endogastrostomy tube placement and surgical jejunostomy in patients with diabetic gastroenteropathy and malnutrition may pose an increased risk for fungal peritonitis. Mycobacterial peritonitis should be considered in patients with apparent sterile peritonitis and lymphocyte predominance. A peritoneal biopsy may be warranted to increase the diagnostic yield. A number of different atypical mycobacterial species have been reported in addition to several different types of mold.

A disciplined approach to peritonitis treatment is essential to optimize outcome and maintain patients on long-term PD. While a number of different treatment approaches utilizing IV, PO, or IP medications have been proposed, a reasonable approach is presented in Figures 6 – 10. From 1993 to 1996, the Peritonitis Working Group shifted the emphasis from vancomycin and ceftazidime to cephalosporin and gentamicin in response to concerns regarding vancomycin-resistant enterococci (VRE). The emergence of VRE in dialysis units has raised critical international health concerns. The major concern relates to the potential for the transfer of the vancomycin resistance (genes) from VRE to other gram-positive organisms such as *Staphylococcus*. Clinical isolates of vancomycin-resistant pneumococci have now been identified. The enterococci species are now the second most frequent cause of nosocomial infections in the US and are increasing in their resistance to vancomycin. The larger the hospital, the greater the percent of resistant enterococci. With < 200 patients the percent of resistant enterococci is 0.6%; this increases to 7.2% with > 500 patients. Patients presenting with VRE are more likely to be malnourished, > 40 years old, have gastrointestinal (GI) abnormalities such as diarrhea and incontinence,

and have a prior history of antibiotic use. Seemingly a single dose of vancomycin should not significantly increase the risk for VRE, but continued use of vancomycin for any subsequent dose when other antibiotics are appropriate is discouraged. Therefore, treatment with vancomycin is reserved for serious infections with hemodynamic compromise, patients with documented allergies to penicillin, and prophylaxis when there is a high incidence of MRSA or methicillin-resistant *S. epidermidis*.

Appropriate use of cephalosporins is also crucial, given their increased use. Several points should be made regarding the use of cephalosporins and aminoglycosides as empiric treatment. Cephalosporins need to be administered in each exchange due to their lack of negative post-antibiotic effect. While some work has described the use of a high daily dose, further study is needed to validate this dosing scheme. Proper dosing of aminoglycosides should be guided by serum levels, although appropriate drug levels do not guarantee against toxicity. Patients who have an increased risk for aminoglycoside toxicity (e.g. diabetics, patients with prior aminoglycoside dosing in the previous 2 months, and individuals with subclinical hearing deficits) should be identified and alternate treatment protocols designed.

The routine use of IP heparin does not appear to affect the overall outcome of peritonitis. Several reports have utilized heparin, urokinase or streptokinase in cases where there is significant fibrin formation during the course of infection. Fibrin may harbor microorganisms and lead to dialysate drain problems.

Gram-positive organisms (Figure 6) can be divided into 4 different categories: enterococci, *S. aureus*, MRSA, and VRE. For *S. aureus* infections, a 21-day course of therapy is indicated. In diabetic or malnourished individuals, prophylactic coverage for fungal infection should be initiated using mycelex trouches, nystatin oral suspension, diflucan or clotrimazole vaginal cream in female patients. If VRE is documented, the patient will most likely be switched to HD and subsequent antibiotic treatment with quinupristin/dalfopristin, chloroamphenical or trimethoprin-sulfamethoxazole (TMP-SMX) employed.

When gram-negative organisms are identified, the antibiotic selection (Figure 7) should be based upon whether there is a single gram-negative (non-xanthomonas) or either *Pseudomonas* or *Stenotrophomonas*. Gram-negative organisms can be classified into oxidase-negative and oxidase-positive infections or lactose-positive. In the setting of pseudomonal infections, 2 drugs are essential for eradication; TMP-SMX is the primary medication used for *Stenotrophomonas*. Aminoglycoside agents should be continued for *Pseudomonas* infections if there is not a significant risk for vestibular ototoxicity.

If yeast is identified on gram stain and culture, the PD catheter should be removed and the patient should be treated with amphotericin and/or fluconazole depending on culture results (Figure 8). Although catheter salvage with treatment has been reported, the course is protracted and may pose significant patient morbidity. Fluconazole may be effective in healthy, well-nourished dialysis patients; however, certain patients not responding to fluconazole should be switched to IV amphotericin even though the organism may be sensitive to fluconazole in vitro. Delay in converting patients not responding to fluconazole and with persistence of abdominal pain and positive gram stain will lead to increased morbidity and mortality.

Patients presenting with multiple organisms and/or enterococcal infections should be treated appropriately with gram-negative, gram-positive, and/or anaerobic coverage. If

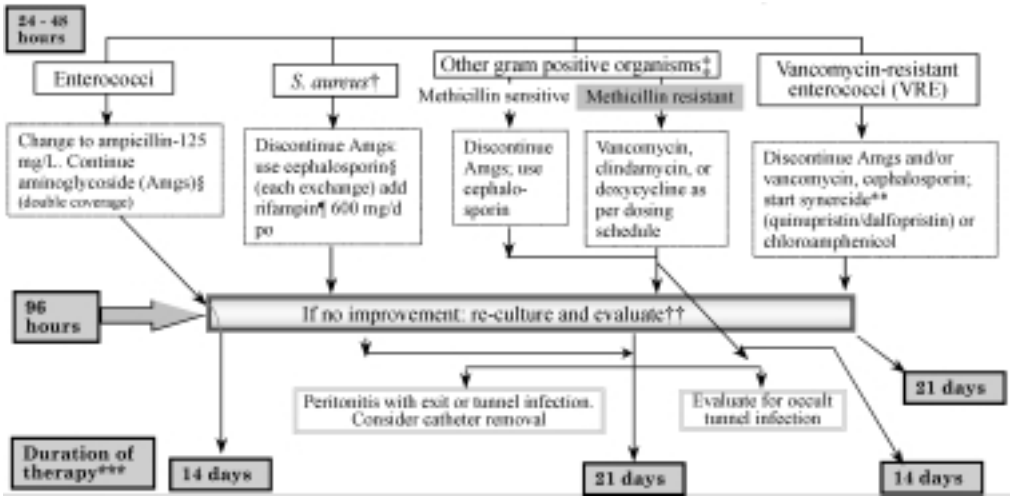


Figure 6. Treatment Algorithm for Gram-positive Organism on Culture. Choice of therapy should always be guided by sensitivity patterns. Avoid prolonged vancomycin use. † If enterocci is resistant to aminoglycoside, use ampicillin alone. ‡ PCN-allergic alternative agents: vancomycin, clindamycin, rifampin, quinolones (ciproflocaxin or ofloxacin). If not PCN-allergic, use anti-staph or 1st generation cephalosporin; if anaphylactoid reaction, use vancomycin. ¶ Ensure normal liver function tests and **NO** lens implants. **Synercide intraperitoneal 1 to 1.5 grams IP in 4 – 6 hours dwell, chloroamphenicol IV 500 mg q 6 hours. †† If methicillin-resistant *S. aureus* is cultured and the patient is not responding clinically, vancomycin or clindamycin plus rifampin should be used. ***Add mycelex trouches for diabetic patients or when total antibiotic treatment > 14 days. Dose mycelex trouches one qid, nystatin (oral suspension) 500,000 IU qid, or diflucan 100 mg qd for entire treatment plus 5 days. For female patients with yeast vaginal infections, use gyne-lotrimin to decrease risk of vaginal candidiasis seeding.

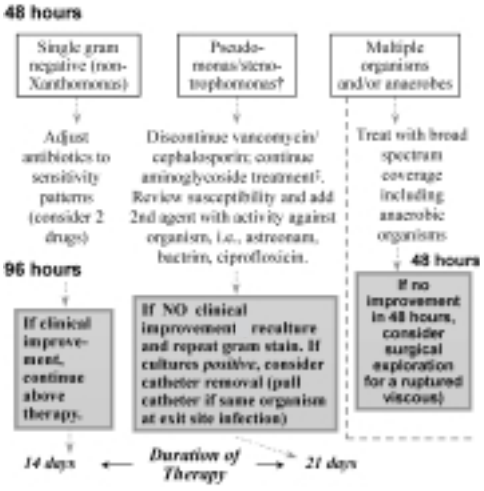


Figure 7. Approach to Gram-negative Organism or Polymicrobial. *(a) Lactose (–)oxidase (–): *Proteus mirabilis, Proteus vulgaris, Providencia* species, *Morganella morganii, Serratia, Salmonella, Shigella, Acine tobacter, Stenotrophomonas*. (b) Lactose (–) oxidase (+): *Pseudomonas aeruginosa, Aeromonas hydrophilia, Moraxella* species, Alcalignes, *Flavobacterum* species, *Hemophilus influenzae*. For *Flavobacteruim*, vancomycin ist the drug of choice. (c) Lactose (+): *E. Coli, Klebsiella, Enterobacter, Citrobacterium*. †For *Pseudomonas* use 2 drugs; for *Stenotrophomonas*, use 1 medication (e.g. trimethoprim-sulfamethoxazole). ‡Continue aminoglycoside unless significant risk for vestibular-ototoxicity. §Cell count **not** decreasing, symptoms persist.

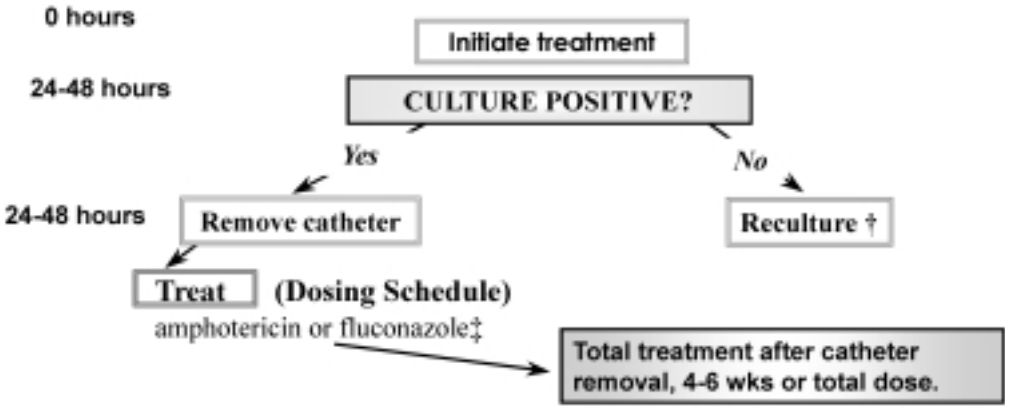


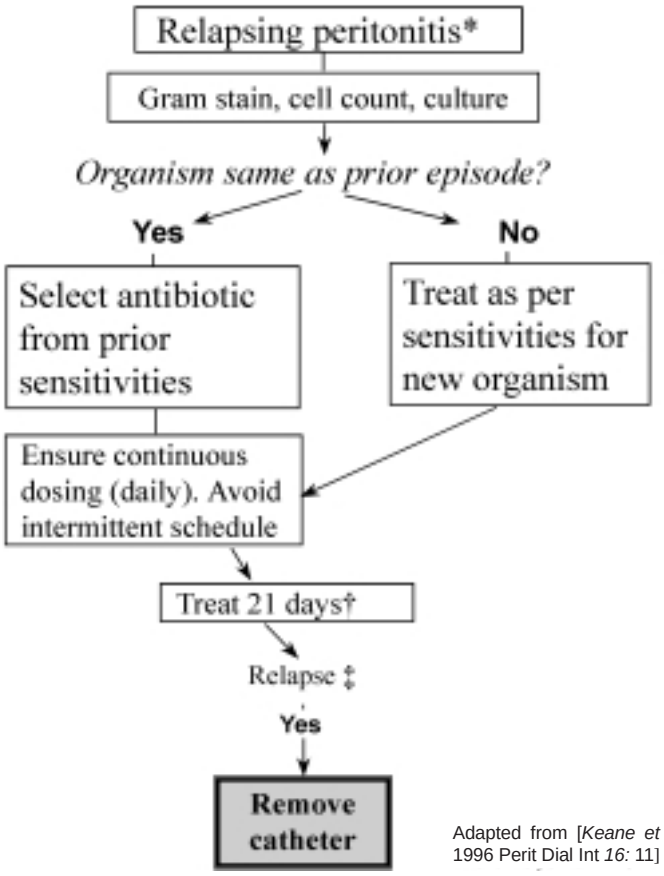
Figure 8. Approach to Fungal Infection in PD – Yeast on Gram Stain (Should see increased % monocytes, significant pain/symptoms) †If symptoms increase and monocytes > 20%, check for acid-fast bacilli. ‡Use fluconazole (200 mg LD, PO then 100 PO daily × 14 days) if Candida albicans; use amphotericin for all other sensitive fungus: total treatment dose IV ≥ 250 mg. Use test dose prior to standard treatment (1mg) dependent on organism sensitivity and infection resolution. A new PD catheter can be inserted in 4 – 6 weeks. Fluconazole may not be as effective as amphotericin, and should be used primarily in healthy, well-nourished dialysis patients. If patient is not responding with fluconazole, convert to IV amphotericin for total treatment course.

there is no improvement in the cell count and clinical status within 72 hours, the patient should undergo surgical exploration because of the high likelihood of a ruptured viscous. While IP free air can be observed on plain films of PD patients, excessive amounts in the setting of persistent infection should raise the possibility of a ruptured viscous. A delay in surgical intervention will lead to a poor outcome in these individuals. Eighty percent of patients developing polymicrobial infections can remain on PD if aggressively treated; the other 22% require catheter removal and transfer to HD.

Abdominal abscesses may complicate peritonitis in CAPD patients, with an incidence of abscess development in 0.7% of peritonitis episodes. Persistent symptoms, IP leukocytosis and culture positivity should prompt a CT abdominal/pelvic evaluation for abscess formation. Draining of the abscess percutaneously or via open surgical procedure will improve the overall patient outcome.

Relapsing peritonitis (Figure 9) is defined as an infection by the same organism < 21 days after treatment. Optimizing sampling and culturing techniques is essential for organism identification. The infection should be treated based upon sensitivities for at least 21 days. Sequential C-reactive protein (CRP) levels have been suggested as a guide for duration of treatment. If a patient relapses with the same organism after a second treatment course, consideration should be given to catheter removal.

Patients utilizing automated PD may present antibiotic dosing dilemmas. Factors that may lead to suboptimal treatment include IP dosing with short dwell times; inappropriate drug levels; low peak to minimal inhibitory concentration (MIC) levels; a short duration of serum levels that exceed MIC or minimal bactericidal capacity (MBC) (intensity index); and delay in conversion to CAPD when IV, IP or PO routes of administration are not effective or practical.



Adapted from [*Keane et al* 1996 Perit Dial Int *16:* 11]

Figure 9. Treatment Approach to Relapsing Peritonitis. *Same organism < 21 days post treatment, recurrent infection: < 21 days with same organism. †Obtain negative culture, normal CRP prior to stopping therapy, add mycelex trouches for duration of treatment and 7 days thereafter. ‡Third bout same organism. If different, individualize therapy; if same proceed to catheter removal.

Catheter Exit Site Infection (CESI)

The rates of CESI and the outcomes of treatment are inconsistent in the literature. Rates may vary from as low as 0.1 – 0.5/patient-year to as high as 1.02/patient-year. This discrepancy may reflect differences in the definition of CESI, chronic and acute care protocols, and treatment of infection once diagnosed. More than 10% of catheter losses occur with CESI. The most common clinical scenarios which result in catheter removal are: the same organism causing CESI and peritonitis, recurrent peritonitis (> 3 episodes same organism), fungal peritonitis, peritonitis with multiple organisms, infection persisting > 3 weeks despite adequate therapy, involvement of the internal cuff documented by ultrasound which has not improved (persistence of peri-cuff fluid) despite antibiotics, and abdominal abscess formation. Both race and climate-specific characteristics may affect infection rates; there is an increased incidence in CESI in tropical climates. Twardowski et al. established 7 different categories of CESI: acute, chronic, external-cuff, equivocal, good, perfect, and traumatized [107]. Table 8 characterizes 4 different CESI categories. The outcome of catheter-related infections depends on the causative organism and degree of inflammation. A significant difference exists

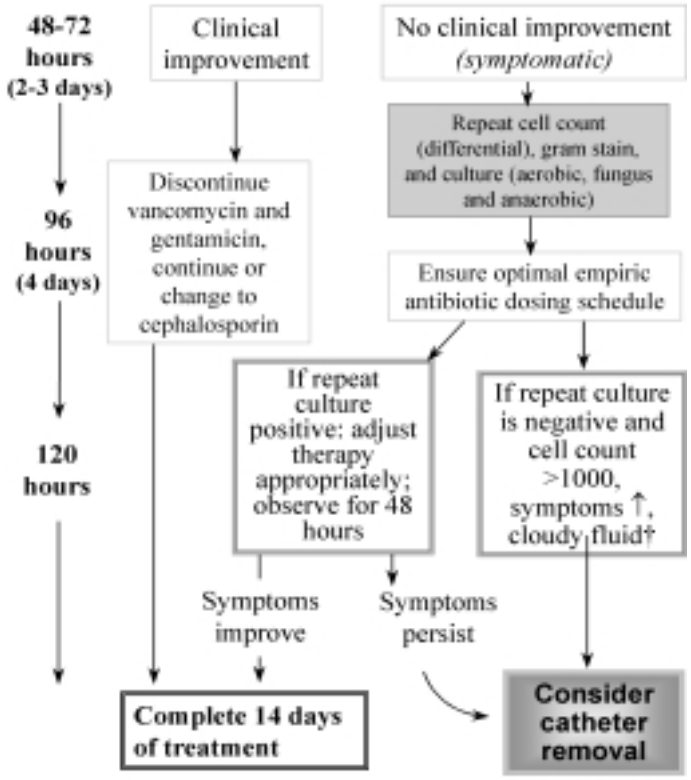


Figure 10. Approach to Culture-negative* Peritonitis. *Consider chemical peritonitis (check for eosinophils; eosinophilic peritonitis, increased cell count with the exclusion of aerobes, anerobes, and fungus). †Discuss with primary nephrologist, consider fungus, acid-fast bacilli, mold (monocytes on differential), or incompletely treated bacterial infection.

between true exit site infections and exit site combined with tunnel/cuff involvement.

Acute infections usually are < 4 weeks in duration, and cause painful erythema at the exit site with a visible sinus tract and usually purulent or bloody external drainage. The acute infection necessitates the cauterization of granulation tissue, and hypertonic saline soaks may improve drainage if purulence is present. When copious purulent drainage occurs, dressings should be changed twice a day. Systemic antibiotics should be empirically started pending culture results if there is a high level of clinical suspicion. The antibiotics may subsequently be adjusted according to the culture and sensitivities. Local antibiotic ointment or solution cannot achieve adequate tissue levels and are usually not effective. Oral cephalosporins or a quinolone (ciprofloxacin 500 – 700 mg/day) may be the initial antibiotics of choice. Exit site infections should be treated for 7 days after there appears to be catheter exit site improvement, with total treatment lasting approximately 10 – 14 days.

Chronic exit site infections have inflammation > 4 weeks. These infections are usually characterized by purulent or bloody external drainage usually greater in amount than during the acute infection phase (Figure 11). Purulence is typically apparent on the dressing. Chronic infections usually lack induration and erythema. Acute changes may occur with trauma, abscess, external cuff seeding, or a second or new organism. Compulsive exit-

Table 8. Management of Catheter Exit Site (CES) Infectious Complications[1]

Classification	Acute (< 4 weeks)	Chronic (> 4 weeks)	Tunnel/cuff infection	Trauma
Appearance	Usually painful erythema > 13 mm, visible sinus tract, purulent or bloody external drainage, possible crust	Widening induration > 13 mm, crust positive, usually sinus tract, (+) dressing drainage, may see proud flesh	Pain over cuff or along tunnel without scab or crust, thick, "gluey/gooey" discharge especially with external cuff	Painful, may have bloody drainage, may be tender over cuff
Diagnosis	Exam culture, gram stain	Exam, culture[2], gram stain, cuff/tunnel ultrasound[3],	Exam, culture, gram stain, ultrasound, cuff/tunnel	History and exam
Exit site management	Cauterize (silver nitrate) granulation tissue, 3% hypertonic saline soaks 5-10 min TID local care: non-ionic surfactant cleansers[4], change dressings BID for significant drainage	Cauterize (silver nitrate) granulation tissue, 3% hypertonic saline soaks 5-10 min TID local care: non-ionic surfactant cleansers[4], change dressings BID for significant drainage	3% hypertonic saline soaks 5-10 min TID, dressing change bid; for copious drainage, may need absorbent dressing, consider unroofing or cuff shaving if external cuff involved	Daily exit care, utilize dressing, use non-irritant cleansers qd
Antibiotic[5]	Start systemic antibiotics, before culture results, adjust when culture sensitivities are available. Treat for 7 days after CES improvement	Utilize synergistic therapy. If standard treatment not successful in 2 weeks, change antibiotics, consider chronic suppressive therapy	Start systemic antibiotics, adjust therapy based on sensitivities and exam	Quinolone or cephalosporin for 5 to 7 days at the time of exit site injury.

(continued on next page)

site local care utilizing hypertonic saline along with cauterization with silver nitrate of granulation tissue is essential. Patients may require synergistic therapy for eradication once the organism is identified. If there is suboptimal response or no change in 2 weeks, antibiotic regimens should be reassessed.

Tunnel or cuff infection pain occurs directly over the cuff or along the tunnel without scab or crust formation at the catheter exit site. The purulence is characterized as gluey or gooey, being thicker than that usually seen with acute inflammation. In some settings, pressure on the cuff will express purulent drainage not apparent at the initial inspection. The outcome of cuff infections is poor despite unroofing and cuff removal. Tunnel infections involving the Dacron cuff are rarely completely cured,

Table 8. continued

Classification	Acute (< 4 weeks)	Chronic (> 4 weeks)	Tunnel/cuff infection	Trauma
Follow-up	Clinic visit every week until improved	Clinic visits every 2 weeks until improved. If drainage persists with induration, consider catheter removal[6]	Evaluate weekly dependent on drainage amount and appearance. Consider cuff un-roofing, cuff shaving if no improvement	Evaluate one week post trauma or sooner if exit site appearance changes

[1]Risks for infectious exit site complications: postoperative hematoma at CES, diabetes mellitus especially with poor glucose control, obesity, positive *S. aureus* nasal carrier, early *S. aureus* infection, early trauma (< 4 weeks post placement) with pain over cuff, dialysate leak at CES, upward exit site, infection < 2 weeks after placement without perioperative antibiotics, gross CES contamination (stagnant or contaminated water). [2]Cultures may be negative if on antibiotics. [3]Povidone iodine (betadine) inactivated by purulent drainage. [4]Examine for pericatheter somnolucent fluid collection (hypoechoic area). [5]Duration of therapy depends on response: cephalosporin for gram positive, quinolone for gram-negative, vancomycin IV or IP for MRSA. If treatment > 2 weeks add fungal prophylaxis: vaginal clotrimazole cream, mycelex trouches, or fluconazole (low-dose). [6]Indications for catheter removal: resistant *Pseudomonas* infection, peritonitis same organism as CES, CES infection with persistent leak, persistent erythema and tunnel infections with positive internal cuff by ultrasound. Modified from Twardowski and Prowant, 1997.

although catheter life can be prolonged with external cuff shaving and systemic antibiotics. Especially in patients awaiting transplantation, it is critical to aggressively treat and document lack of cuff involvement and resolution of tunnel edema. Ultrasound may be helpful in evaluating the internal or deep cuff, and appears to be better than WBC scanning in identifying tunnel infections. Hypoechogenicity indicating a fluid collection, > 2 mm in width along any portion of the catheter track is problematic. Several reports have now demonstrated the usefulness of ultrasound looking for a pericatheter sonolucent fluid collection in the area of the cuff as a predictor of catheter loss, with a higher incidence of detection of tunnel infections (0.35 episodes/patient-year with ultrasound compared with 0.12 episodes/patient-year by clinical criteria). If there is a significant decline of the hypoechoic area around the cuff, then chances are greater for recovery. If there is a decline of < 30%, the vast majority of catheters will be lost. Plum et al. noted that no patient with a negative ultrasound examination underwent surgery for infectious complications, while 69% of catheters with tunnel inflammation on sonographic examination had to be removed [86]. When the ultrasound indicated a tunnel infection, peritonitis rate was significantly higher: 1.7 episodes/patient-year vs. 0.64 episodes/patient-year.

Both the type of cultured organism and the extent of inflammation (i.e. involvement of internal cuff segment) are prognostic factors for the outcome of infection. Because of the indolence in morbidity of *S. aureus* site infections, these patients should undergo sonographic evaluations to determine the level of involvement and chance for eradication. *S.*

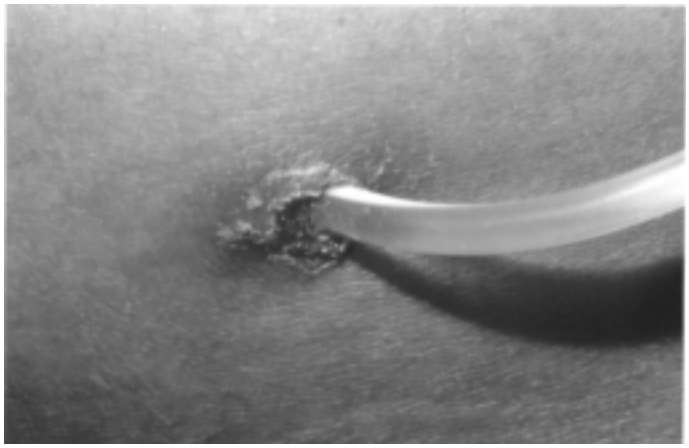


Figure 11. This chronic catheter exit site infection is characterized by persistently purulent external drainage with little or no induration and erythema.

aureus and *Pseudomonas* infections are the most serious infectious organisms causing chronic inflammation and/or eventual catheter removal.

Traumatized exit sites are usually noted by patients due to pain and bleeding, or a change in exit site appearance. Since infections can occur in 2 – 4 days, patients should be started on antibiotics and daily non-irritant cleansers. Quinolones or cephalosporins may be started at the time of injury and continued for 5 – 7 days to decrease the risk of cuff infection and catheter loss. Patients with acute, chronic, or tunnel infections, or trauma should be followed closely until resolution.

Subcutaneous cuff removal in persistent exit site or tunnel infections can significantly reduce catheter loss related to infection. If partially exposed or palpable within 3 cm of the exit site, the cuff may by removed by blunt dissection under local anesthesia at the bedside (Figure 12).

A number of local care antiseptic solutions (hypertonic saline, povidone iodine, sodium hypochlorite, chlorhexidine, dilute hydrogen peroxide) have been used to resolve or prevent CESI. With hypertonic saline therapy, 4 – 5 gauze pads soaked with warm 3% saline are applied 3 times daily for 5 – 10 minutes for 2 – 4 weeks followed by once daily thereafter. Several reports have examined the use of chlorhexidine vs. povidone iodine and noted a significant decrease in the frequency of CESIs with the former treatment. Povidone iodine ointment or cleanser offers some protection against CESIs, but the benefit is apparently limited to approximately 140 days following the start of PD and may be neutralized if an acute infection with purulent discharge develops [111]. Twenty-three to 45% of cases using povidone iodine turned positive for microorganisms within 24 months. *S. aureus*, *S. epidermidis* and *Pseudomonas* are the most common organisms seen. Alternating the catheter exit site care in patients at risk especially after 3 – 4 months of povidone iodine would be a reasonable option. Sodium hypochlorite and sodium chloride are effective against a broad spectrum of organisms (including *S. aureus* and *Pseudomonas*) with rapid killing in one minute and prevention of reinfection. Partial electrolysis of sodium chloride (Amuchina) to eliminate sodium hy-

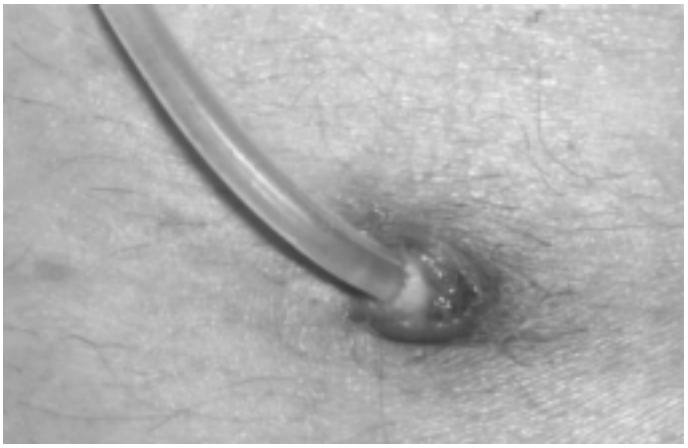


Figure 12. An infected, partially exposed Dacron cuff can result in recurrent or non-healing catheter exit site infections. The cuff can be removed at the bedside with blunt dissection under local anesthesia.

droxide may increase efficacy and decrease the toxicity of standard sodium hydrochlorite.

Antibiotic selection is crucial in all these types of infections. A Consensus Committee of the International Society of Peritoneal Dialysis on peritoneal catheter and exit site practices towards optimum peritoneal access (1998 update) [34] noted that in patients with gram-positive organisms, oral penicillinase-resistant penicillins, cephalexin, or TMP-SMX should be utilized. Unless a patient had a history of MRSA, vancomycin should be avoided. In *S. aureus* infections, rifampin 300 mg twice daily (BID) in adults or 5 – 10 mg/kg BID in children should be administered. With gram-negative infections, ciprofloxacin 500 mg BID should be used until the exit site is normal. The outcome with ciprofloxacin for the treatment of CESI was significantly better than with other antibiotics with a mean recovery of nearly 50%; however its use is contraindicated in children. IV and IP treatment can be considered if the resolution is slow with PO treatment.

In patients with mycobacterial, pseudomonal, or xanthomonal infections, differences may exist in the subsequent risk for peritonitis and catheter removal. *Xanthomonas*, although associated with other microorganisms in 66% of cases, is less likely to lead to peritonitis and catheter replacement than pseudomonal CESIs, which are usually severe and require IV or IP antibiotics [83]. Altogether, 83% of CESIs resolved with PO ciprofloxacin, 17% required catheter removal, and 22% developed *Pseudomonas* infection several months after apparent resolution of CESI. These findings highlight both the resiliency of *Pseudomonas* and the importance of infection prevention.

Patients with prior infections are seemingly more prone to develop cuff infections in the future. Prophylactic antibiotics for 3 – 6 weeks after catheter placement, timely diagnosis and elimination of *S. aureus* nasal carrier states, effective use of non-soap and water catheter exit site care and avoidance of trauma are essential to decreasing CESIs. Sterile dressings for at least 6 weeks also tend to improve outcome. Mupirocin ointment applied at the exit site significantly lowered the incidences of *S. aureus* CESIs (86% decrease) and peritonitis (reductions of 69% for *S. aureus* peritonitis and 38% for all peritonitis),

as well as the catheter removal rate attributable to *S. aureus* infections [75]. The use of a silver ring did not appear to be effective in preventing exit site infections in a randomized, multicenter, clinical trial. Ultraviolet (UV) radiation may be helpful in eliminating bacteria as demonstrated in a small study (68 patients) in which 10/18 cases receiving UV radiation became culture-negative.

Chronic tunnel infections in children and adults may justify simultaneous removal and replacement of the CAPD catheter [89]. The catheter should be placed on the contralateral side with the internal cuff in the midline using the same entrance to the peritoneal cavity. Dialysis can be resumed immediately after the operation with low volumes. Only 4/23 pediatric patients in one clinical experience relapsed within 3 months, with the main causative agent being *S. aureus*. Automated PD can be started within one day of catheter placement and continued for 7 days with low volumes in patients who have previously been on CAPD. Utilizing this technique, patients in 38/40 procedures could successfully continue PD. Some surgeons may elect to create a new entrance on the contralateral side. Simultaneous removal and replacement should occur only if there is no evidence of active infection. Patients should receive 3 – 6 weeks of antibiotic prophylaxis. Further work in this area is needed to define the best approach.

S. aureus Nasal Carriage

The relationship between nasal carriage and risk of CESI and subsequent peritonitis is still controversial. The Danish Study Group of Peritonitis in Dialysis [117] and other studies reported that *S. aureus* infections occurred significantly more frequently among carriers in both HD and PD. In general, nasal carriage *S. aureus* is associated with risk of postoperative wound infection and of exit site infection in patients on chronic PD and intermittent HD. The Danish group found 59.5% of HD patients and 51.2% of CAPD were *S. aureus* carriers. Permanent carriage was usually primary nasal (44% HD, 34.9% CAPD), with rare skin carriage alone. Nasal carriage appears to be associated with a much higher rate of CESI. The incidence of infection was higher in diabetics (26.3% vs. 10.3% in non-diabetics), even though diabetics were not significantly more frequent carriers (60.5 vs. 55%). The higher infection rate despite similar carrier rates may suggest that diabetics are at higher risk for *S. aureus*, and need aggressive treatment. Luzar et al. noted that 45% of their patients and 77% of diabetic patients were nasal *S. aureus* carriers before catheter insertion [64]. CESI occurred in 0.4 episodes/patient-year in carriers and 0.1 episodes/patient-year in non-carriers. *S. aureus* carriage has also been found more often in patients with previous *S. aureus* peritonitis. Interestingly enough, one-half of spouses were carriers, with the same phage type and carrier state. Thus, the carrier state seems unrelated to age, gender, and presence of DM. Twenty-eight of 167 patients had MRSA nasal carriage in one study. The patient drop-out rate from infection for MRSA was comparable to pseudomonal and fungal infections, but significantly higher than methicillin-sensitive *S. aureus*.

CESI does not always result from nasal carriage, and most exit site infections occurred among patients without previous *S. aureus* colonization. And yet based upon a number of studies, eradicating *S. aureus* nasal carriage even in patients with one positive culture may decrease the risks for CESI and subsequent peritonitis. The quest for prophylaxis rather than treating individual episodes is spurred by the suboptimal current treatment of *S. aureus* with significant risk for relapse and catheter loss. Several studies have evalu-

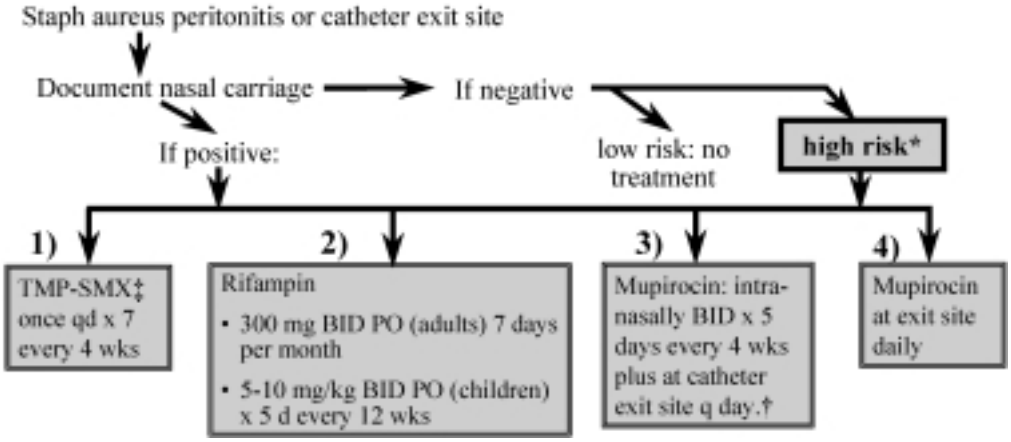


Figure 13. Prophylaxis for S. aureus: Initiate therapy (1, 2, 3, 4) for: culture positive (nasal carriage), *high risk patients** (> 65 years of age, diabetes, serum albumin < 3.0 mg/dL, second S. aureus infection) or if S. aureus rate > 40% of all CES infections; *low risk*, no therapy.
†Except in patients with polyurethane catheters. ‡TMP-SMX: trimethoprim-sulfamethoxazole.

ated varied prophylactic techniques to prevent the development of *S. aureus* CESIs in both children and adults (Figure 13). Certain strategies may increase the risk for complications (i.e. rifampin results in the development of resistance when given alone), and patients will likely need periodic retreatment or cycling with antibiotics to eradicate the carrier state. The greatest impact of prophylaxis with TMP-SMX was evident during the first 3 months of therapy. Local application of antibiotics at those areas most noted for colonization, i.e. naries and PD access port, resulted in only temporary bacterial elimination. Mupirocin, predominantly bacteriostatic in action, is bacteriocidal at the higher concentrations achieved following topical application, and was effective in terminating the normal carrier state in 65 – 100% of cases. Nasal mupirocin (calcium mupirocin 2%) administered twice daily for 5 consecutive days every 4 weeks was demonstrated in a large multicenter study to reduce the rate of exit site infection. Mupirocin calcium ointment 2% and cyclic oral rifampin 600 mg for 5 days every 3 months are equally effective in reducing *S. aureus* catheter infection, however many patients discontinue rifampin due to side effects. Even though resistance may occur with mupirocin, the selection of mupirocin-resistant clones is slow and stepwise. While application of mupirocin in MRSA may lead to increased resistance, particularly because of the presence of the MEC gene associated with multiple antibiotic resistance, applying the mupirocin ointment 3 times a week rather than daily may offer less risk for resistance.

Antibiotic Toxicity

Varied individual plasma clearances and risks of drug toxicity argue for obtaining drug levels for patients receiving vancomycin and/or aminoglycosides. Vestibular toxicity due to aminoglycosides in PD patients may be of more concern because of the relatively steady state serum levels believed to be more toxic than the high peak serum levels followed by very low trough levels seen with

intermittent dosing. Although some studies note no association between ototoxicity and serum aminoglycoside levels, others have shown that both high peak and high trough levels are correlated to ototoxicity. Approximately 12.5% of ototoxicity results from the use of aminoglycosides. In 46 dialysis patients, Antonelli et al. found that older patients had significantly longer auditory nerve and brain stem conduction times, indicating a subclinical disorder of the auditory nerve function which might increase risk for ototoxicity [5]. The current recommendation is to screen for high frequency auditory abnormalities and vestibular ocular reflex dysfunction in high-risk patients prior to aminoglycoside use, since the toxic effect of aminoglycosides is additive.

The toxic effect of vancomycin on the cochlea of CAPD patients is rare if serum levels are monitored closely. Tinnitus and high-tone hearing loss are recognized complications of vancomycin therapy and are frequent antecedents to deafness. Damage to the auditory nerve, initially affecting high-frequency hair cells, then middle- and low-frequency hair cells, is irreversible, although toxic changes may be delayed for weeks or months after exposure. Damage is determined more by the cumulative level rather than by the daily dose. Vancomycin administered in combination with an aminoglycoside may be synergistic in producing ototoxicity.

Quinolones, increasingly used for the treatment of infection, have several clinically significant drug interactions. Quinolones may inhibit the metabolism of certain drugs, and when given concomitantly with divalent or trivalent cations, the action and concentration are reduced. Quinolones increase serum theophylline and caffeine concentrations; and combination with warfarin raises the INR (the international anticoagulant marker). Magnesium sulfate/aluminum antacids, iron, enteral feedings, calcium (Ca) products and zinc decrease the absorption of quinolone, and should not be taken at the same time.

Cardiovascular Disease

Overview

The most common cause of death in ESRD is cardiovascular disease, accounting for nearly 50% of deaths in US patients. Cardiovascular complications that can occur in PD include myocardial structural abnormalities, valvular abnormalities, increased risk for arrhythmias, lipoprotein alterations, vascular disease, autonomic impairment, hypotension, hypertension, pericardial disease and modality-specific risk factors for vascular ischemia. To date no study has convincingly demonstrated that patients on CAPD are at greater or less risk of cardiovascular, peripheral-vascular or cardiovascular events when compared to individuals on HD. Bloembergen et al.'s analysis of data from the United States Renal Data System (USRDS) demonstrated that ESRD patients treated with PD had a 19% higher adjusted mortality risk than those treated with HD, with a third of the excess mortality stemming from myocardial infarction (MI) and cerebrovascular accidents (CVA) [10]. More recent analysis of these data by Vonesh et al. refuted this finding and demonstrated that the only cohort at potentially greater risk on PD was diabetic females over the age of 55 years [109]. Other studies have shown no difference or a higher risk in HD compared to PD. Port et al. examined possible factors that may have an impact on the observed outcome differences between PD and HD [87].

Myocardial Structural Complications

Both progression and regression of left ventricular hypertrophy (LVH) have been described in patients on PD. Differences in hydration, methodology, and hypertensive control could all be contributing factors. Progression of LVH has been correlated to increased blood pressure (BP) and cardiac index. Hypercirculation secondary to hypervolemia theoretically will negatively affect blood pressure control in PD especially in diabetic patients. Abnormal left ventricular filling, impaired aortic elasticity, increased peak systolic pressure, increased stroke work index, and higher cardiovascular systolic volume may all contribute to LVH in PD patients. Non-survivors are more likely to have lower left ventricular ejection fractions and higher cardiovascular systolic volumes (pump dysfunction) compared to survivors. One can also see impaired diastolic left ventricular function even without LVH, perhaps due to increased cytosolic Ca^{+} and ultrastructural changes characterized by cardiac fibrosis with interstitial proliferation and expansion. While LVH can develop in patients on PD, clinically there a significantly lower left ventricular end diastolic pressure, left ventricular end systolic volumes, stroke index and cardiac index, and a higher mean velocity of circumferential fiber shortening in PD compared to HD. These physiologic events may explain why LVH is present in approximately 52% of patients on CAPD, but 93% on HD [3].

The actual PD prescription may adversely affect cardiac function in certain patients. The higher the dialysate dwell volume in patients with LVH, the greater the alteration in left ventricular internal dimensions due to increased intra-abdominal pressure. Systolic function decreases in such individuals with infusion of 2.5 – 3 L volumes. This effect of intra-abdominal pressure on cardiac performance is especially important in PD patients with severe hypertrophic cardiomyopathy. These individuals may experience a decrease in cardiac preload if IP volumes > 2.5 L are instilled. Hypotension may result during the dwell phase when intra-abdominal pressure is highest, possibly reducing venous flow to the heart. In animal models a step-wise increase in intra-abdominal pressure results in a graded decrease in cardiac output. Findings in several dog experiments have demonstrated that intra-abdominal pressure > 20 mm Hg decreases cardiac output and causes a redistribution of regional blood flow. In most settings where UF rate is slow, there should be no significant effect on cardiac preload.

The two risk factors independently associated with the development of LVH are systolic hypertension and older age. When evaluating the impact of pressure on LV mass, Harnett et al. noted the mean systolic BP in the group who developed LVH was 150 ± 13 mm Hg, compared to 137 ± 16 mm Hg in controls [39]. BP is significantly lower on PD than on HD over time. Hajjar et al. [38] in a crossover study of 68 patients who changed dialysis modalities demonstrated a 16 mm Hg-increase in BP in patients moving from PD to HD and a 14 mm Hg decrease in patients moving from HD to PD.

Anemia also plays a role in increased LV dilatation and LV mass. Although left atrial chamber volume, and LV mass and chamber volume decrease with good BP control, structural abnormalities occur if hypertension is untreated when receiving erythropoeitin (EPO). While gender may affect certain mediators of LVH in dialysis patients, little is known about the impact of PD vs. HD on these factors. Previous reports demonstrated that both baseline LV mass and cavity volume were strong predictors of late mortality in patients with uremia. Both LV dilatation with normal systolic and high cavity volume (>

120 mL/m^2) and low mass-to-volume ratio (> 1.8 mL/m^2) were independently associated with late mortality in uremia. Daily dialysis with PD may optimize structural modeling as compared to intermittent therapy with HD. LVH may be a frequent finding in children on dialysis. PD may offer a lower risk of development of LVH, especially in younger children.

Interestingly, protein-calorie malnutrition (loss of approximately 40% of initial body weight) has been proven to adversely affect the heart. In animal experiments loss of subcutaneous fat stores, reduction of myocardial glycogen content, myocardial atrophy and interstitial edema (increased myocardial water content, along with the formation of intracardiac edema) from malnutrition may compromise cardiac function and survival. These findings can occur in patients with cardiomyopathy on PD who suffer from continued cardiac cachexia despite aggressive PD regimens. Dialysis alone may not reverse the sequelae of end-stage heart failure.

Valvular Abnormalities

Sclerosis or calcification of the mitral valve or annulus is associated with decreased survival in PD patients. This may be related to a high calcium-phosphorus (Ca × P) product or the use of standard Ca rather than low Ca dialysate over long periods of time. Historically, mitral calcification was favored by longstanding pre-dialysis arterial hypertension, and by a high Ca × P product during PD. Decreased survival with mitral calcification results from decreased systolic left ventricular function or severe valvular incompetence. There is now a well-documented correlation between serum Ca, a high Ca × P product, and the risk of calcified aortic stenosis. Therefore, inadequate Ca control in PD might add to the already existent cardiac risk seen in ESRD.

Arrhythmias

Arrhythmias are frequent among the dialysis population [103]. Twenty-four percent of patients demonstrate > 10 ventricular ectopic beats/hour, with 11% noticing episodic atrial fibrillation, and 8% ventricular tachycardia. Heart block occurs in < 2%. Overall, 51% of patients demonstrate arrhythmias on Holter monitoring. On autonomic testing, 61% had abnormal heart rate responses, while 63% had abnormal BP responses. These changes support a causal relationship between arrhythmias and autonomic neuropathy, which is exacerbated by dialysis. Canziani et al. noted a significantly decreased incidence of mild and severe arrhythmias in PD compared to HD patients [14]. Factors which may be linked to ventricular arrhythmias on PD are age, LV mass index, and an abnormal LV wall score.

Ventricular tachycardia, ventricular fibrillation, torsades de pointes and long QT syndrome have been reported in patients taking Cisapride alone or in combination with a number of other medications (e.g. erythromycin, clarithromycin, fluconazole, and ketoconazole) that inhibit cytochrome P4503A4. Cisapride should not be used in PD patients with a prolonged QT interval at baseline, those with a history of torsades de pointes or those with long QT syndrome. It should also be avoided in patients with sinus node dysfunction and in those with second or third degree atrioventricular block.

Atherosclerosis and Hyperlipidemia

Because cardiovascular disease continues to be the main risk for death in patients on dialysis, many reports have been published in the past decade on modality-specific lipoprotein differences (total levels, clearance rate,

receptor modification, particle size, transport). CAPD increases total cholesterol, triglyceride, total cholesterol to HDL ratio, and apolipoprotein-B to apolipoprotein-A (apoA/apoB) ratio [100, 114]. The overall clearance of LDL is markedly less in CAPD vs. HD, with a fractional catabolic rate for LDL of 0.268 ± 0.072 pools/day in PD vs. 0.376 ± 0.045 in HD [45]. This may be due to alterations in LDL structure or the LDL receptor itself. Decreased binding may be attributed to an increase in advanced glycosylation end products or a chemical modification due to uremia itself. The apoB/apoA ratio is significantly higher in diabetic vs. non-diabetic ESRD patients. Furthermore, the dialysis modality may alter distribution of the LDL particle size, possibly as important a risk factor for atherogenesis as absolute LDL levels. In a study of 65 ESRD patients, 48% of the CAPD patients had small LDL particle size vs. 23% for HD patients [82]. Lipoprotein clearances correlate with molecular mass, plasma concentration and dwell times, with a preferential clearance of HDL in PD amounting to approximately one-third of the daily synthetic rate. The mean daily clearance of $apoA_1$, a major HDL protein, is twice that of apoB, which is the predominant protein associated with LDL.

Lipoprotein A (Lp(a)) may be a genetic marker for increased coronary artery disease (CAD) risk in both dialysis and nondialysis patient cohorts, and may vary by country and ethnic or racial group. Lp(a) values are clearly affected by the mode of the renal replacement therapy, being highest in CAPD. The vascular significance of Lp(a) may depend not only on the actual level but also on the presence of procoagulant factors [58]. Patients with CAD had higher fibrinogen concentrations (628 ± 59 mg/dL) and higher Lp(a) concentrations (43.5 mg/dL). Petersen et al. examined anticardiolipin antibodies and Lp(a) levels in 22 PD and 64 HD patients [85]. The mean Lp(a) level on PD was 56.7 mg/dL and 38.8mg/dl on HD (NS). All patients who suffered an MI or CVA had Lp(a) levels > 30 mg/dL.

Patients with increased peritoneal membrane transport characteristics demonstrate a more atherogenic lipid profile. Heimburger et al. demonstrated that the increased Lp(a) in CAPD was related to the peritoneal glucose absorption, and peritoneal membrane type [40]. The importance of carbamylation and glycosylation on lipoprotein atherogenicity in CAPD is undetermined. The presence and concentration of advanced glycosylation end (AGE) products may increase the risk for atherosclerosis in PD. AGE-modified LDL levels may represent a particularly atherogenic form of LDL. AGE-LDL as well as AGE peptides are likely to contribute to the development of atherosclerosis in diabetic patients. There is a strong correlation between serum total cholesterol and the AGE-LDL (AGE apoB and AGE-lipid). The development of new dialysate solutions may ameliorate lipoprotein abnormalities in ESRD patients, since a positive correlation appears to exist between glucose absorption from the dialysate and Lp(a) values. Also hypoalbuminemia, especially in the high-transport group, appears to be an important trigger for the elevation of Lp(a) in CAPD. Seemingly, this may be a modifiable risk factor. Lp(a) is significantly decreased by regular infusions of albumin. Yet, a 6-month prospective crossover study evaluating the effect of one postprandial 1.1% amino acid dialysate demonstrated no effect on dyslipidemia in CAPD patients [73].

Red blood cell (RBC) transport may also play a role in the lipoprotein abnormalities observed in PD. The decreased transfer of cholesterol between RBCs and the antiatherogenic HDL fraction may hinder transport from peripheral tissues and result in increased

atherosclerosis risk. In ESRD patients on dialysis, low levels of plasma HDL-3 cholesterol levels, HDL-3 phospholipid content and net transport of RBC cholesterol-2-isolated HDL were significantly lower compared to controls.

A number of reports have examined whether the dialysis technique itself changes lipid profiles in long-term CAPD patients. In a group of 16 stable nondiabetic PD patients with initial total cholesterol < 230 mg/dL, total cholesterol triglyceride HDL, LDL, and apoB/apoA_1 did not show significant changes by serial measurements from 6 – 13 months following initiation of PD [53]. There was no relationship to Lp(a) levels and time on CAPD.

Aortic pulse wave velocity (A_0PWV) and aortic calcification were also examined in CAPD patients to try to estimate risk of accelerated atherosclerosis. While lipid values did not denote patients with progressive vascular disease, A_0PWV increased in 46% of patients. The degree of abdominal aortic calcification was divided into two separate categories, with the greatest calcification seen in patients on CAPD > 5 years. It is unclear whether these findings are modality-specific or related to uremia since HD patients were not prospectively examined.

A meta-analysis comparing the efficacy of various antilipidemic therapy for PD, HD and transplant patients demonstrated the effectiveness of β-hydroxyl-β-methyl glutaryl Cofactor A (HMG-CoA) reductase inhibitors in lowering abnormal lipid patterns. A number of medications are effective in treating dyslipidemias in CAPD as described by Massy and Lye [65, 67]. Both statins and fibric acid derivatives have proven effective, although individual differences mandate monitoring of lipid levels. Target treatment lipoprotein levels may need to be further decreased to control vascular atherosclerosis in dialysis patients. Both Nevalainen and Lahtela reported that IP insulin, while achieving better glycemic control in PD and improved insulin sensitivities as compared to subcutaneous (SC) administration, results in increased serum triglycerides and total cholesterol and decreased HDL cholesterol – possibly due to a direct effect of IP insulin on the liver [60, 77].

While the levels of Lp(a), total cholesterol, and LDL may increase in CAPD, the lipoprotein patterns from CAPD patients may exhibit a resistance to in vitro oxidation, a possible step in the development of atherosclerosis. Podrez et al. noted that Lp(a), but not LDL, is oxidized in plasma of CAPD patients [266]. It is unclear whether Lp(a) is more prone to oxidation than LDL. Another possibility is that Lp(a) is preferentially oxidized in renal failure patients due to its lower plasma clearance as compared to LDL. Since Lp(a) binds better to epithelial cells and platelets than LDL, it is possible that such binding can facilitate Lp(a) oxidation in vivo.

A retrospective review of 53 pediatric PD patients likewise showed a high incidence of hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and associated low levels of HDL unchanged while on PD [95]. As with adult PD patients, their risk for future atherosclerosis may rest with not just the lipoprotein levels, but rates of oxidation and effects of newer nonglucose dialytic solutions.

Abnormal Vascular Pro-ischemic Factors

The risk for thrombosis, from both vascular calcification and loss of autoregulation leading to altered flow, could increase ischemic events. Key components of the fibrinolytic system are tissue plasminogen activator

(TPA) and the fast-acting inhibitor of TPA plasminogen activator inhibitor (PAI). In uremic patients, lipoprotein abnormalities and derangement of the fibrinolytic system with increased PAI levels may contribute to the development of atherosclerosis obliterans (ASO) or cardiovascular disease (CVD). TPA and PAI are synthesized and secreted by vascular endothelial cells. Thus, in damaged vessels there would be a slow, continuous release of TPA and PAI. Plasma fibrinogen, PAI activity, and factor C are significantly elevated in CAPD patients, while TPA is increased in both HD and PD. These data raise concerns regarding the risk for increased thrombosis on PD vs. HD [18]. This risk might be modified by the use of less hyperosmotic dialysate, optimization of albumin levels, control of hypertension, and treatment of lipoprotein values with HMG-CoA reductase inhibitors. A comparison of CAPD patients with and without ASO with controls [56] showed significantly depressed serum albumin and HDL concentrations on CAPD, with a markedly elevated ratio of total cholesterol to HDL. CAPD patients with atherosclerosis had higher fibrinogen, total PA and PAI levels vs. normal and CAPD patients without atherosclerosis. TPA level was an independent predictor in a stepwise fashion for ASO. Serum albumin was inversely correlated to fibrinogen; however, no relationship to TPA and PAI was detected. There was no significant difference in certain lipids, lipoprotein and apolipoprotein values in male diabetic patients on CAPD. Female PD patients' levels of triglyceride apolipoprotein, apoB, low density lipoprotein (LDL), and cholesterol/HDL ratio were all significantly higher than those in normal females. Plasma levels of fibrinogen and von Willebrand factor (vWF), but not PAI, were higher both in the male and female compared to controls. The hypoalbuminemia in many dialysis patients may account for an increase in fibrinogen synthesis.

Ecosaenoid precursor (arachnidonic acid and ecosapentanoic acid) levels have been evaluated in CAPD patients with and without DM. Arachnidonic acid levels were significantly higher, while eicosapentaenoic acid (EPA) levels were significantly depressed in CAPD patients [43]. The lowest EPA values are found in Type I (insulin-dependent) DM CAPD patients. The combination of increased arachnidonic acid, lack of N-3 fatty acids, and reduced prostaglandin-12 biosynthesis lead to a higher formation rate of thromboxane A2, which may promote atherogenesis via vasoconstriction and platelet aggregation. Therefore, in addition to the typical dyslipidemias found in CAPD patients, high levels of Lp(a) and fibrinogen may contribute to the elevated risk of CAD and other cardiac complications.

Hyperhomocysteinemia is a well-established, independent risk factor for atherosclerosis, and thromboembolic and vascular disease, especially in ESRD. Hyperhomocysteinemia (> 16 μmol/L) is observed in PD, while homocysteinemia is more intense (29.8 μmol vs. 19.9 μmol) and prevalent (90.8% vs. 67.4%) in HD as compared to PD patients [81]. Diabetic PD patients should be screened and aggressively treated with high folic acid doses when elevated levels of homocysteine are detected.

Vascular Disease Patterns

Vascular disease in CAPD patients is a major cause of death. Arterial calcifications, composed primarily of Ca salts found chiefly in the internal elastic lamina of the intima and in the media of the arterial walls, generally tend to progress in patients with ESRD. Whether arterial calcifications occur during dialysis due to the procedure, or just to the

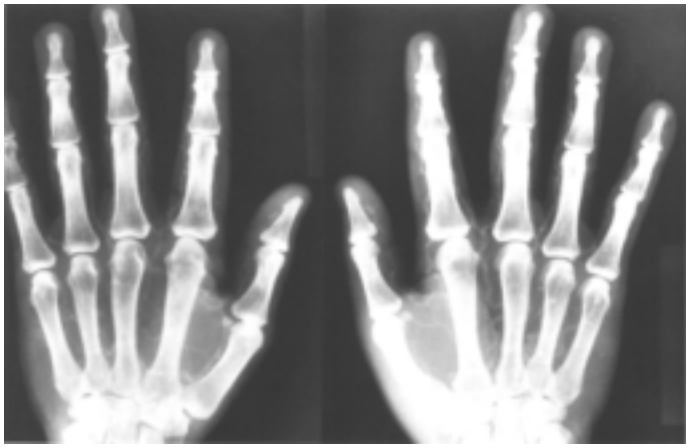


Figure 14. Peripheral (digital artery) vascular calcifications can occur in patients on PD, as demonstrated in this 42-year-old female on PD for six years.

greater prolongation of life in the presence of chronic renal failure is unclear, although on average, vascular calcification starts approximately 9 years after onset of ESRD. Peripheral vascular calcifications, once established, may progress on both HD and PD. Lipid deposition, intimal hyperplasia, and thrombosis cause vascular damage, with endothelial damage mediated via smooth muscle cell migration and proliferation, secretion and synthesis of extracellular matrix (e.g. collagen, glycosal-aminoglycan, glycoprotein, and elastin), and platelet disruption with thrombosis. Deep vessel wall injury associated with reduced fibrinolytic activity and increased PAI activity may lead to intravascular thrombosis and impaired thrombus resolution. Two primary patterns of vascular calcification occur: axial (aortic and iliac in femoral vessels), and peripheral (digital arteries) (Figure 14). Most patients have evidence of both types while on dialysis. Furthermore, the presence of these vascular calcifications decreases vessel compliance and may reduce autoregulation distal to a stenosis in the coronary bed. In prior studies age, systolic BP, hyperparathyroidism, plasma phosphorus (P), and vitamin D were principal determinants of severity in the rate of progression of vascular calcifications.

Rheologic factors (blood flow, vessel radius, pressure gradient, and blood viscosity) may contribute to atherogenesis, thrombosis and ischemia both centrally and peripherally. Atherosclerotic patients have statistically significant increases in blood plasma viscosity compared to normal controls. Therefore, in a calcified vessel with both an inability to autoregulate and high plasma viscosity, thrombosis may occur in the presence of increased procoagulant concentrations. In the setting of endovascular injury from blood pressure and hyperlipidemia, thrombosis may lead to obstruction, lack of distal autoregulation, and tissue infarction.

A large proportion of patients reported with progressive vascular calcifications have DM, and all of the diabetics in the study by Meema et al. developed calcifications [70]. The same study demonstrated no differences in serum Ca and P, Ca × P product, parathyroid hormone (PTH), and alkaline phosphatase levels. Other studies have shown a correlation between serum Ca or the Ca × P product and the risk of calcified aortic stenosis. Increased arterial stiffness and cardiac overload were linked to severe coronary arterial calcifications and an increase in arterial pulse wave velocity.

Vascular calcifications may contribute to decreases in distal blood supply and, combined with peripheral sensory and autonomic neuropathy, may affect oxygen and nutrient delivery to tissues causing ischemia, ulceration, infection, and need for amputation. More than 69,000 major lower extremity amputations for ischemia were performed in the US in 1989 [25]. The higher the amputation rate, the higher the mortality rate. The incidence of lower extremity amputations among patients on HD was estimated to be 2.9% for unilateral amputations and 1% for bilateral amputations. Few data exist for PD cohorts. ESRD has a serious adverse impact on hospital mortality and long-term survival rates after amputation. The most common causes of death following amputation are cardiac events. ESRD patients were more likely to have CAD than non-ESRD patients (78 vs. 42%). The prophylactic value of hygiene of ischemic lower extremities is illustrated by a 3-fold decrease in amputation rates in patients with diabetes who participated in a foot education program.

Stroke is the third leading cause of death in the general population, with an even greater risk in the ESRD population. The risk of death for stroke may actually be greater for patients on PD vs. HD despite a lower prevalence of preexisting cerebrovascular disease and better control of BP, according to USRDS data [68]. The risk for death from stroke on PD compared to HD was nearly 2-fold greater for elderly, diabetic, African-American, and female patients. It is not clear whether this difference might reflect established cerebrovascular disease at dialysis initiation or an actual dialysis modality effect. Moreover, stroke mortality itself is related to factors such as inadequate dialysis, uncontrolled hypertension, and hypervolemia. Therefore a major issue is whether the modality itself or its prescribed use affects the death rate from stroke in ESRD patients. Considering the risk for progressive atherosclerosis in ESRD, identification of high-risk patients and aggressive treatment are indicated.

Avoiding coronary artery events is extremely critical especially in diabetic patients on PD. The FINMONICA myocardial infarction registry study [72] demonstrated that in 3442 patients, 45% of all diabetic men and 38.8% of all diabetic women with their first MI died within one year. These figures contrasted with 32.5% for nondiabetic males, and 22.1% for nondiabetic females. A substantial portion (28% of the males and 10% of the females) of these deaths occurred outside the hospital. Aggressive treatment with antilipidemic drugs, identification of patients with procoagulant risk, and intervention for critical lesions amenable to angioplasty and stenting, and/or cardiac revascularization should be implemented.

A major difference in death rate from myocardial ischemia and infarction exists between the United Kingdom and Italy in both the overall renal replacement therapy and the HD group [61, 92]. In males on PD, the disparity between countries is more subtle. For both primary renal diseases and diabetic nephropathy, the EDTA registry data for PD and HD demonstrated relatively lower cardiovascular mortality in the PD compared to HD patients; however, the relative cardiovascular mortality remains constant by modality over the last decade. Identifiable predictors of progression include: DM (accelerated, significant stenosis); interval between MIs; angina severity; chest pain with exercise; test endpoint; location of lesion in proximal right coronary artery (RCA), mid RCA, or mid left anterior descending artery (LAD); and stenosis morphology (single vs. tubular). Diabetic lesions tend to be more tubular than single, with disease localized to the RCA and LAD. Because of diabetic PD or HD patients'

increased risk for CAD, they should undergo regularly scheduled screening.

Hypotension

The prevalence of hypotension in CAPD patients varies in different populations from 10 – 15%, with hypovolemia causing 25% of these cases [1]. A study from the Toronto Hospital noted approximately 12% of the CAPD population developed hypotension. Twenty-five percent of the patients had hypovolemia as the etiology, 23% heart failure, 18% antihypertensive medications, and 34% unknown etiology. The mortality rate was higher among hypotensive patients than among nonhypotensive patients on PD. Physiologic night-time declines of BP ("dipping") were more significant and pronounced in PD than in HD. Those that appear most susceptible to hypotension are patients with demonstrated autonomic neuropathy, LVH, diastolic dysfunction, inappropriate activation of cardiac reflexes and abnormal vascular response.

Cardiovascular autonomic impairment can affect the peripheral circulation as well as the heart in dialysis patients and this may have implications for cardiovascular homeostasis. A comparison of peripheral blood flow responses and sympathetic vasoconstrictive reflexes in CAPD patients with matched control subjects has been previously reported [47]. Cardiac autonomic function assessed by standard tests of heart rate variability (deep breathing, Valsalva maneuvers and standing from a lying position) was significantly impaired in patients on PD compared to controls.

The QT_C interval may be used in the evaluation of autonomic neuropathy as a marker of venous tone reactivity. The main defects leading to hypotension are decrease in venous tone or increase in venous pooling of blood, decrease in overall venous return, and thus cardiac output. Proamitine (mitodrine hydrochloride) may help some cases of hypotension by acting selectively on venous and arterial α_1-adrenergic receptors without stimulating cardiac β-adrenergic receptors, thereby increasing venous tone and decreasing venous capacitance.

Cardiomyopathy secondary to right ventricular failure, ischemia, transplantation and its sequelae, viral infections, and infiltrative amyloidosis can also result in hypotension. Increasing numbers of cardiomyopathy patients with renal dysfunction and diuretic resistance are now starting PD for daily volume removal and the lower levels of hemodynamic stress on PD vs. HD. Anticoagulation may be needed to avoid thrombotic cerebrovascular complications, given the low flow, depressed cardiac output, persistent hypotension, and potential for arrhythmias in these patients. Cardiomyopathy secondary to amyloidosis is a contraindication to the use of digoxin, and calcium channel and beta-blockers.

Patients on PD may have a risk for uremic pericarditis due to inadequate dialysis (poor prescription design). Infective pericarditis documented by technetium^{99} scan following peritonitis has been reported.

Musculoskeletal Complications

Hypocalcemia, Hypercalcemia, and Hyperphosphatemia

Significant interest has been generated by the effects of varied dialysate Ca concentrations on serum Ca and PTH levels, renal bone disease management, and regulation of phosphorous (P) levels with medication on PD.

Hyper- and hypocalcemia are complications commonly observed in patients on PD. Ca mass transfer in PD depends on dialysate Ca concentration, ionized serum Ca, and the UF rate [115]. Fifty percent of patients with persistent hypercalcemia and hyperphosphatemia who were changed to low Ca dialysate achieved significant decreases in both Ca × P product and percent hyperphosphatemia. Ca balance is positive if dialysate Ca is ≥ 2 mEq/L. One and one-half percent dialysate results in an approximately 9.8 mg Ca uptake, whereas 4.25% led to a loss of 21 mg. Standard peritoneal dialysate has a relatively high Ca concentration of 3.5 mEq/L, which may result in hypercalcemia [113]. A number of studies have stressed the effect of different dialysate Ca concentrations on Ca fluxes in PD. Bro et al. showed that plasma PTH levels could be adequately controlled during a one-year follow up using 1.35 and 1.25 (but not 1.75) mM/L Ca dialysate concentrations without either hypercalcemia or the use of aluminum-containing phosphate binders [11]. In a 6-month multicenter study of 103 patients, total Ca was significantly lower (9.6 vs. 10.8 mEq/L), immunoreactive calcium (i-Ca) was depressed (4.76 vs. 5.15 mg/dL), and there were fewer episodes of hypercalcemia in patients using low Ca dialysate. Chagnac et al. found a 71% increase in Ca values when the dialysate Ca was further reduced from 1.25 to 1.0 mEq/L [19]. The decrease in dialysate Ca did not prevent the observed increased serum Ca, suggesting that lowering the serum PTH value reduces the ability of the bone to handle a Ca load within a few weeks. For severe hypercalcemia (serum Ca > 13 mg/dL), hospital pharmacies may need to prepare 0 mg/dL-Ca dialysate.

Kurz et al. [59] assessed the effect of differing dialysis modalities on Ca turnover in 57 HD and 38 CAPD utilizing tracer kinetic studies with ^{45}Ca orally and ^{47}Ca intravenously. Elevated PTH levels were found in 91% of all patients, whether on PD or HD. Serum concentrations of 25-hydroxycholecalciferol and alkaline phosphatase were markedly lower in CAPD than HD, and CAPD patients were less responsive to the action of immunoreactive PTH. A randomized, multicenter, controlled trial with 103 stable CAPD patients compared low-Ca (1.0 mM/L) vs. higher-Ca (1.75 mM/L) dialysate. All patients received oral Ca carbonate and calcitriol, and those with increased Ca were treated with aluminum hydroxide. Patients treated with low-Ca dialysate showed a 3-fold decrease in the incidence of hypercalcemia, with PTH levels > 2 times normal in 40% of cases.

Technetium^{99m} etidronate bone scan alterations progressed with time on dialysis especially in younger patients and those with higher intact PTH levels. Aggressive early treatment with optimal control of PTH is essential to avoiding bone disease with chronic renal failure (CRF), and for patients just starting PD. Maintianing a lower Ca will permit the administration of more Ca carbonate to control phosphate. This may be less of a problem with development of Renagel (sevelamer hydrochloride) which is a polymeric oral phosphate binder.

Hypocalcemia can occur in PD and is related to decreased oral intake, low vitamin D levels, dialysate Ca mismatch or after parathyroidectomy postoperatively. Decreased oral intake of Ca may lead to profound hypocalcemia and or tetany on PD.

Using standard CAPD volumes, approximately 10 mM of phosphate are removed per day with 2-L, or 15 mM/day if using 3-L volumes. Only high volume CAPD can cause a negative phosphate balance over a one-week period. Hyperphosphatemia can occur in PD and is primarily related to dietary intake of P, and noncompliance in taking P binders. While hypophosphatemia can occur on PD, it is un-

common. The main causes are refeeding in malnourished PD patients, overzealous phosphorous binder administration, inadequate intake, and secretory diarrhea.

Low-turnover Bone Disease (Adynamic Bone Disease)

Advanced renal failure may lead to either a high bone turnover (osteitis fibrosa) or low bone turnover. Three different groups of low-turnover bone disease occur in ESRD patients on dialysis: osteomalacia, aluminum-related, and adynamic lesions. In PD, osteomalacia is uncommon due to supplemental vitamin D. Low-turnover aluminum bone disease is also on the decline due to the use of nonaluminum-containing phosphate binders. Adynamic bone disease is characterized by low bone turnover, normal or low osteoid volume, and decreased bone formation rate, resulting in increasing numbers of microfractures and increasing the risk for clinically-apparent fractures. The diagnosis of adynamic bone disease is supported by normal or low PTH, unremarkable aluminum levels, higher ionized Ca, lower alkaline phosphatase, and a higher incidence of calcifications. The vascular calcifications seen with adynamic bone disease in PD patients may be secondary to hypercalcemia from lower skeletal Ca retention and lower plasma Ca efflux due to older age. Significant hypercalcemia and metabolic encephalopathy can occur especially in diabetic patients on PD and may not respond to a reduction of Ca in the dialysate. In this setting a bone biopsy should be performed to rule out a high turnover condition [31]. Unfortunately, the use of PTH levels did not predict the degree of bone turnover in half of the CAPD patients with values between 65 – 450 pg/mL. Low-turnover bone disease without aluminum toxicity is associated with secondary hyperparathyroidism, DM, hyperphosphatemia, hypocalcemia, altered vitamin D synthesis, impairment in PTH secretion and metabolism, and possible down-regulation of the renal PTH/PTHrP messenger RNA receptor. Moreover osteoblast type I collagen messenger RNA (mRNA) expression is lower in cells from adynamic bone vs. bone from hyperparathyroid states.

Adynamic bone lesions accounted for 50% of bone lesions seen in 268 dialysis patients described by Sherrard, and is more common in PD vs. HD (61% vs. 36%) [99]. Hutchinson et al. reported histologic abnormalities more commonly in older patients with a longer duration of dialysis (10 vs. 7.1 years), although 28% of patients had the lesion at the start of dialysis [46]. In an additional study, 31% of CAPD patients demonstrated adynamic or aplastic disease at the outset of treatment or within 12 months of starting PD. The management of adynamic bone disease should be directed to stimulating PTH to values 2 times normal.

Moderate hyperparathyroidism with intact PTH from 150 – 903 pg/mL can be effectively treated using 0.5 mg to 1.5 mg calcitriol twice weekly. Ca levels should be monitored and hypercalcemia treated by a transient reduction in dialysate or oral Ca intake. Vitamin D should be stopped for Ca levels > 11.5 mg/dL or 2.9 mM/L. Pulse therapy is contraindicated with the serum P > 6 mg/dL or 1.9 mM/L, with a plasma PTH < 120 pg/mL. In pediatric patients the use of high-dose pulse IV, IP or PO calcitriol therapies significantly decreases the serum PTH levels and retards the formation of osteitis fibrosis. Calcitriol decreases the synthesis and secretion of PTH by a direct effect on PTH gene transcription, as well as suppressing PTH by increased intestinal Ca absorption. Oral and IV bolus pulse calcitriol therapy are equally effective in suppressing PTH. Hyperphosphatemia can be aggravated

by suppression of PTH in some cases. A new drug, $^{19}nor_1$alpha-25 dihydroxy vitamin D_2, can suppress immunoreactive PTH levels, but does not have as great an effect on serum Ca and P levels. This difference in effect may be linked to a smaller affinity for the vitamin D receptors with less mobilization of Ca from the bone than calcitriol, and less affinity for vitamin D binding protein. Treatment of hyperparathyroidism must be carefully balanced, as it may lead to the development of adynamic bone lesions with oversuppression of PTH and increased Ca intake or hypercalcemia in certain cases.

The vast majority of patients on chronic dialysis demonstrate histologic evidence of osteodystrophy. The long-term implications of this are unknown.

Dialysis-related Amyloidosis

The dialysis-related amyloidosis characterized by β-2 microglobulin amyloid deposition appears not to be a consequence of dialysis treatment alone, but rather a complication of CRF initially recognized in patients receiving long-term HD. This consequence can also occur in PD but the small number of patients on PD for > 10 years limits the risk [17]. The histologic prevalence of musculoskeletal β-2 microglobulin amyloid deposition increases with duration of dialysis from around 20% at 2 years for HD, to 100% after 13 years, although β-2 microglobulin amyloidosis can be seen in patients who have not started therapy.

β-2 microglobulin's high affinity for collagen explains the predominance of joint and bone disease. β-2 microglobulin amyloidosis deposits are preferentially deposited in bone, articular cartilage, synovium, and ligaments. Only the number of bone lesions is significantly correlated with patient age and negatively correlated with residual renal function. Patients characteristically present with a triad of symptoms with shoulder pain (scapulohumeral periarthritis), carpal tunnel syndrome, and flexor tendon deposits in the hands. The diagnosis can be made from X-ray, ultrasonography and/or scintigraphy with radiolabelled β-2 microglobulin scanning using radiolabelled serum amyloid P. Hand lesions are found in 85% of patients with dialysis-related amyloidosis. Synovial thickening may be shown on sonography and positive scintigraphic imaging delineates the presence of dialysis-related amyloid. A rotator cuff thickness > 8 mm and echogenic pads between muscle groups of the rotator cuff are strongly suggestive of β-2 microglobulin. The presence of at least one of these two findings in ultrasonography of the shoulder provides a relatively sensitive and highly specific noninvasive adjunct to the clinical diagnosis of β-2 microglobulin amyloidosis in the patient undergoing long-term dialysis. However, identification of β-2 amyloid by Congo red staining of biopsy specimens, or centrifuge synovial fluid sediments remains the gold standard for diagnosis.

The pathogenesis of β-2 microglobulin amyloidosis is incompletely understood. Several important contributing factors include levels of β-2 microglobulin, limited proteolytic cleavage of β-2 microglobulin, modification of β-2 microglobulin and other proteins with AGE, and elevated circulating levels of proinflammatory cytokines. Only renal transplantation may slow or halt the progression of β-2 microglobulin amyloidosis. PD and HD do not appear to arrest its development. Preservation of residual renal function early on in PD may be helpful in avoiding accumulations of β-2 microglobulin, and may have a long-term impact in avoiding this condition once patient has been transferred to HD. It is unclear whether the incidence, prevalence and rate of progression of β-2 mi-

croglobulinemia differ according to dialysis modality. It is essential that amyloidosis be prevented by removing the β-2 microglobulin by dialysis, to counterbalance the β-2 microglobulin amyloid generation. In comparing HD, hemofiltration or CAPD, metabolic studies with radiolabelled β-2 microglobulin indicated a slight increase in β-2 microglobulin synthetic rate in uremic patients irrespective of dialysis technique (4.49 ± 2.60 vs. 2.68 ± 1.3 mg/kg/day) [78]. More recent pharmacologic agents, e.g. antiamyloid fibril (anthracyclin-4-iodo-4-deoxydoxoribirin) may help in amyloid load reduction.

Erosive Azotemic Arthropathy

Another uncommon bone lesion that may occur on PD is erosive azotemic osteoarthropathy (EAO). EAO typically occurs in the distal interphalangeal joints of the hands, and has a higher prevalence in HD vs. PD (19% vs. 6%). Affected patients tend to be older with a history of carpal tunnel syndrome. EAO is not related to severe secondary hyperparathyroidism.

Dialysis patients are at risk for a low bone mineral density (BMD) osteopenia as a consequence of hyperparathyroidism, acidosis, secondary amenorrhea, chronic hepatitis, and aluminum exposure. Dual energy X-ray measurements of BMD showed significantly higher values in PD vs. HD (0.985 vs. 0.94 g/cm^2). BMD may increase with time on dialysis. While still abnormal, CAPD patients have better bone mineral metabolism than HD patients. Little has been written regarding BMD osteopenia in the PD population, however there does not appear to be an increase in osteopenia in patients on PD.

Diabetic PD patients are at greater risk for aluminum deposition compared to nondiabetic patients. Even small amounts of aluminum-containing phosphate binders can increase the risk for aluminum deposition on bone surface compared to nondiabetics. Therefore it is essential to avoid all aluminum-containing binders in diabetic patients with hyperphosphatemia.

Carpal Tunnel Syndrome

Carpal tunnel syndrome occurs in 14% of patients on PD. Nomoto et al. examined records from 5050 patients undergoing PD in Japan between 1980 and 1993 [79]. Only 7 developed carpal tunnel syndrome. All 7 were females. Two to 31% of patients on HD are afflicted with carpal tunnel syndrome. Benz found 18% in a 5 – 97-month follow up of CAPD patients [8]. Apparently CAPD minimizes the emergence of carpal tunnel syndrome with its characteristic pain, numbness, and tingling in the hands. Amyloid could be a causative factor in CAPD carpal tunnel syndrome. However, β-2 microglobulin levels were markedly lower in CAPD vs. HD patients, and yet, they were greater than those seen in normal patients. This may be directly related to preservation of residual renal function on PD and more optimal middle molecule clearance.

Myopathy/Calcifications

PD patients may develop muscle weakness, decreased endurance and easy fatigue. While the etiology is complex, both vitamin D and carnitine deficiencies have been implicated. Vitamin D deficiency is one of the causes of uremic myopathy in PD. Although vitamin D administration causes symptomatic relief, electromyography (EMG) abnormalities (polyphasic motor nerve unit potentials of brief duration and decreased amplitude and

fibrillation potentials) may not significantly change. The effectiveness of proponyl, used to improve strength, is open to debate.

Carotene deficiency has also been linked to myopathy in PD patients. While carotene deficiency can result in defective oxidative ATP synthesis, there is little evidence to suggest that skeletal muscle metabolism is affected by PD. Patients with anemia and those patients engaging in anaerobic exercise do not respond clinically to propionyl-L carotene supplementation [105]. Moreover, oxidative metabolism did not normalize with carotene administration, suggesting anemia and carotene deficiency are not the only causes of mitochondrial dysfunction leading to myopathy in PD.

Extraskeletal calcifications (Figure 15) have been associated with an increase in Ca-P product, excess PTH, and extracellular fluid in PD patients. Two main types of extracellular calcifications can occur: visceral and periarticular. There is an association between large soft tissue Ca deposits and aluminum intoxication. Metastatic calcifications, sometimes multiple, can be detected by bone scintigraphy technetium^{99m} methyldiphosphonate (MDP). Several reports have demonstrated a beneficial effect of diphosphonate (disodium ethan-1-hydroxy, 1-diphosphorates) on reduction of tumoral calcinosis in PD and HD.

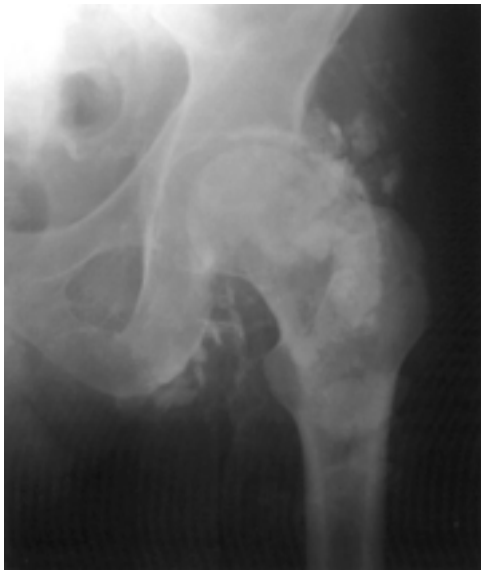


Figure 15. Periarticular extraskeletal calcifications can occur in patients on PD associated with an increase in calcium P product and excess PTH. Patients may demonstrate significant symptomatology from these calcifications.

Back Pain

A number of patients on PD may develop lower back pain. Usually these individuals have alterations in body posture resulting from accentuation of lumbar lordosis due to intraperitoneal dialysate. This alters normal spinal mechanics, and leads to pain. Those factors which may contribute to adverse effects on lumbar lordosis are prior multiple abdominal surgeries, previous disc disease, spondylosis, spondylolithesis, and long-standing metabolic bone disease. Regular lower back strengthening exercises, attention to appropriate posture, the McKenzie rehabilitation program, and change to cycler therapy with the majority of treatments performed in the supine position may be effective in reducing pain.

Other Issues: Fluoride, Tendon, Oxalate

A single report has demonstrated an increase in fluoride levels in CAPD despite appreciable clearance across the peritoneum (3.1 ± 1.97 vs. 2.5 ± 1.37 μm/L). Increased serum fluoride is associated with a lower risk of osteodystrophy in ESRD.

Patients on PD can develop tendon inflammation, rupture or capsular tear. The longer a patient is on dialysis and the more severe the metabolic abnormalities, the greater the risk. These clinical events can occur independently of β2 microglobulin deposition.

Patients on PD may develop hyperoxalatemia resulting from oxalate retention. Levels of oxalate in PD patients are 3 – 5 times greater than normal. PD clears approximately 300 μM/day, approximately equal to the normally synthesized amount. Even when a steady state is achieved, serum levels are usually elevated. Usually those patients who develop hyperoxalatemia as a complication on PD are consuming excessive amounts of vitamin C; 100 mg of ascorbic acid increases oxalate by 20%. Concomitant administration of "high dose"vitamin B_6 will decrease but not normalize serum oxalate levels.

Pulmonary Complications

Patients on PD may develop a number of pulmonary complications. These include hydrothorax, pulmonary function abnormalities, pulmonary edema, bronchopulmonary infections, metastatic calcifications, and sleep dysfunction.

Hydrothorax

The prevalence of hydrothorax ranges from 1.6% [21] to 2.9% [80] to as high as 10% [98]. In many cases, patients are either placed on HD temporarily or undergo permanent transfer. Eighty-eight percent of acute hydrothorax in CAPD occurs on the right side from one day to 8 years after the initiation of PD. Seventy-four percent of patients present with dyspnea, while 26% are asymptomatic. Most patients are female, multiparous, and have been on PD for variable periods of time. Patients with polycystic kidney disease are at increased risk for hydrothorax. Peritonitis may also increase the risk, possibly related to a disruption in the continuity of the peritoneal-pleural structure. Approximately 6% of hydrothorax patients suffer peritonitis just prior to the development of hydrothorax. Several reports have indicated hydrothorax occurs after coughing. Hydrothorax can be diagnosed by the finding of a pleural effusion on chest X-ray. Further work-up consists of peritoneal-pleural scintigraphy, or contrast peritonography with non-ionic contrast (25 m/L). Thoracentesis yields fluid with a transudate protein concentration < 30 g/L, low lactate dehydrogenase (LDH), pleural glucose > plasma glucose, and the presence of both D and L lactate isomers. (Plasma normally contains only the L isomer.) Methylene blue installation, used in the past, is unreliable.

The standard approach to treatment, successful in 38% of cases, is temporary transfer to HD. Pleuradesis is required in 16%, and 46% must be permanently transferred to HD. Surgical exploration of patients with hydrothorax demonstrates localized areas of pleura separated from the diaphragm forming blebs. With the increased intra-abdominal pressure or changes in intrapleural pressure with coughing, dialysate could rupture the blebs, allowing fluid to enter the pleural cavity. Videothoracoscopy allows identification of the diaphragmatic defect. If amenable to repair, talc is placed under direct visualization, allowing even distribution over the inferior surface of the lung. Pleurodesis can also be accomplished by IP autologous blood instillation (40 mL) followed by the Fowler position for 2 days. Fibrin adhesive has also been used to repair diaphragmatic defects.

Therefore, the therapeutic options for patients suffering hydrothorax include: permanent transfer to HD; temporary transfer to HD with retrial of PD; conversion of patient to diurnal PD with an empty supine nighttime exchange; pleuradesis with talc, tetracycline, or fibrin glue; and surgical closure or repair using Teflon patches.

There has been one reported case of tension hydrothorax as a complication of continuous cycling PD. This occurred in the setting of massive hydrothorax producing hemodynamic compromise.

Respiratory Function Abnormalities

The various pulmonary function abnormalities reported in PD most likely would only affect patients with underlying parenchymal lung disease, e.g. COPD, IP pressure > 20 cm of water and a decrease in vital capacity (VC) > 25% [35]. Infusion of dialysate in PD patients without lung disease decreased expiratory reserve volume (ERV) 21% (1.00 to 0.79 L) and functional residual capacity (FRC) 12% (2.60 to 2.28 L). Inspiratory capacity (IC) increased 13% (2.08 to 2.34 L) when the abdomen was full, due to increased diaphragmatic contractility because of the elevation and lengthening of the fibers of the diaphragm [90, 91]. In another study, as PD volume increased from 0 to 3 L, FRC decreased 2.41 to 1.493 with mean total diaphragm length index increasing from 0.22 to 0.28 and diaphragm radius curvature remaining unchanged. Respiratory muscle strength increased as a function of dialysate volume, reaching its maximum after the infusion of 3 L.

CAPD patients may experience a mild but clinically insignificant decrease in carbon monoxide transfer compared to pre-dialysis or HD groups despite adequate correction of uremia and anemia. Small airway collapse with subsequent ventilation-perfusion mismatch and arterial hypoxemia may occur if the FRC decline from intra-abdominal dialysate falls below the closing volume of the lung. Two-liter dialysate volumes cause a significant reduction of alveolar partial pressure of oxygen (pAO_2) and the alveolar-arterial oxygen gradient ($A\text{-}aO_2$), but no effect on airway resistance. Subsequent diaphragmatic adaption, with a right shift in the force-length relationship, limits the “true” reduction in lung volume, pAO_2 and alterations in respiratory muscle strength during chronic dialysis.

Hospitalized infants on ventilators may be more susceptible to the pulmonary consequences of intra-abdominal fluid than adults or adolescents. Mid-dwell peak IP pressure correlates with a significant decrease in pulmonary compliance and an increase in airway resistance in infants on PD. In children on CAPD, the routine filling of the abdomen is followed by an 11% decrease in residual volume, which is not significant. Even though lung volumes are frequently reduced in CAPD, they do not change noticeably during dialysis itself. Overall reductions in inspirametric values are minor, as assessed through plethysmographic lung volumes, airway conductance and single breath carbon monoxide transfer factor.

Bronchopulmonary Infections

Patients on PD are at increased risk for bronchopulmonary infections due to depression of the humoral and cellular immune systems, reduced macrophage activity of increased interstitial lung fluid if over-hydrated, altered $A\text{-}aO_2$ gradient, and reduced ventilation in the lung base. This makes aggressive diagnosis and treatment of bacterial pulmo-

nary infections crucial to avoid significant morbidity.

Metastatic Pulmonary Calcifications

Metastatic pulmonary calcifications can occur in patients on PD. Usually these are asymptomatic and undetectable by conventional radiology methods until severe disease exists. Pulmonary calcifications occur in up to 80% of patients having undergone dialytic therapy. They may rarely evolve to pulmonary fibrosis, cor pulmonale, and severe respiratory insufficiency. Calcifications may be diastrophic, metastatic, or idiopathic associated with Ca, P, and metabolic disorders with precipitation of Ca salts within the parenchyma of the lung.

Pulmonary Edema

Pulmonary edema may occur in CAPD secondary to a number of interacting factors. The most common is prescription mismatch where the dialysis regimen does not optimally match the transport characteristics of the peritoneal membrane. Usually this occurs soon after initiation of dialysis and prior to performing the formalized PETs. Pulmonary edema occurs more frequently in the context of left ventricular failure, cardiomyopathy and acute ventricular infarction, especially if severe anemia and hypoproteinemia are present.

Sleep-related Respiratory Disorders

Sleep-related respiratory disorders in PD patients are frequent, with 73% reporting insomnia, and 52% reported unintentional napping during the day [110]. Clinically significant sleep apnea was present in 13.6% of patients. The effect of PD on sleep-related respiratory function might result from dialysate bulk load in the abdomen causing alterations in the metabolic control of respirations during sleep. In patients with typical sleep apnea, pAO_2 was significantly lower during the night for PD vs. non-PD patients. In apneic patients, higher dialysate drain volumes in the morning were correlated to lower minimum arterial oxygen saturations during the night. Individuals with documented or suspected sleep apnea should have a formal evaluation, including arterial oxygen saturation during sleep while on PD. Prospective PD candidates with a history of sleep apnea symptoms should undergo formal testing prior to starting PD.

Metabolic Complications

Acid-base Abnormalities

Approximately 50% of patients with renal failure on PD experience a number of acid-base abnormalities. Many of these are directly related to the type of dialysate used during PD. Acid-base balance (ABB) in CAPD patients can be summarized by the equation:

ABB = dialytic base gain – metabolic acid production – urinary losses – interstitial ABB.

Dialytic base gain depends on peritoneal buffer fluxes, which is the only source of buffer for CAPD patients. The net bicarbonate gain per exchange is a function of bicarbonate content in the dialysis solution, dwell time, UF rate, and arterial plasma bicarbonate [30]. While metabolic acidosis is more common in HD, PD patients may develop bicarbonate

levels < 24 mM/L (cut-off values vary 22.0 ± 4 mM/L). Metabolic acid production as a function of protein catabolic rate and dialysate base gain is the most important factor for the body's base balance. When plasma bicarbonate concentration decreases due to an increase in metabolic acid production, bicarbonate loss through standard lactate CAPD solution decreases, leading to a greater positive dialytic base gain. When an increase in daily net UF is required for clinical reasons, a decrease of dialytic base gain occurs leading to a decline in plasma bicarbonate concentration and worsening metabolic acidosis.

Chronic metabolic acidosis decreases albumin synthesis, induces negative nitrogen balance, and leads to increased protein catabolism and branch-chain amino acid metabolism. Sodium bicarbonate supplementation in PD patients increased the serum bicarbonate from 19.3 to 26.2 mM/L, thus decreasing leucine oxidation and protein turnover, and correcting acidosis [36]. PD patients using standard dialysis fluid lactate concentrations of 35 mM/L can develop mild acidosis, which activates the ATP-dependent ubiquitin proteolytic pathway. This negative buffer balance can be corrected by increasing the lactate concentration to 40 mM/L. Serum bicarbonate or total CO_2 < 19 mEq/L is deleterious to bone and muscle metabolism and is a marker of increased mortality. The frequency of metabolic acidosis is higher in patients with lower transport characteristics. Lactate gain, duration of PD, CRP and normalized protein nitrogen appearance (nPNA) were independent factors determining the arterial bicarbonate level.

Discrepancies in the reported prevalence of metabolic acidosis in PD patients is most likely due to differences in the concentrations of dialysate lactate (40, 37 or 35 mM/L) and prescribed dwell times. Dialysate/plasma (D/P) creatinine is positively correlated with gain of lactate and dialytic base, and arterial bicarbonate concentration. Since the molecular weight of lactate is 89 daltons compared to 113 daltons for creatinine, high transporters have less metabolic acidosis. The effluent bicarbonate concentration can be predicted from the patient's plasma bicarbonate concentration and the net UF rate for dwell times ≥ 4 hours or more prolonged dwell time. Bicarbonate dialysate improves acid-base homeostasis in CAPD, and future bicarbonate solutions may dramatically affect levels of protein turnover.

Peritoneal dialysis effluent pH is decreased in CAPD peritonitis even in the absence of a positive culture, provided the cell count is elevated. In gram-negative peritonitis, the peritoneal effluent is more inflamed and abnormalities persist longer resulting in a marked increase in pCO_2.

Lethal lactic acidosis from the oral hypoglycemic agent, Metformin, in a diabetic female PD patient has been reported. Moreover, D-lactate-containing dialysate may raise serum D-lactate to abnormal levels in PD. Using dianeal with a D-lactate concentration of 26 mM (range 19 – 27 mM), led to serum D-lactate levels in CAPD patients 4-fold higher than controls [4]. Usually lactate does not increase significantly unless there is severe hepatic failure leading to inadequate conversion of lactate to bicarbonate. With metabolic or respiratory alkalosis, patients on PD are unable to compensate due to the presence of lactate in the dialysate. If this occurs, patients may need HD or treatment with hydrochloride.

Electrolyte/Mineral Disorders

Metabolic alkolosis can lead to hypocalcemic tetany in PD by decreasing the amount

of Ca in the ionized form. The risk is highest in PD cases after parathyroidectomy. Pulmonary parenchymal disease, e.g. COPD, also poses a risk by predisposing CAPD patients to developing respiratory alkalosis from hypoxia with "fixed" bicarbonate levels that do not allow for an unlimited degree of hyperventilation. Treatment with O_2 or ammonia chloride may help avoid alkalemia. Lastly, low-Ca dialysate may result in alkalosis and hypomagnesemia in certain cases.

Hypokalemia

Approximately 36% of CAPD patients develop hypokalemia requiring supplemental potassium (K^+). Approximately three-quarters of the IP-administered K^+ is absorbed. Supplementation of 20 mEq/L is generally well tolerated [101]. The effect of IP K^+ concentration on serum levels depends on the D/P concentration gradient; with greater degrees of K^+ depletion, the incremental increase from IP K is smaller.

In a study of hypokalemia in CAPD patients, individuals who subsequently required K^+ supplementation had significantly lower initial serum levels (3.6 ± 0.65) vs. 4.0 ± 0.6 mEq/L), complained more of weakness, and were more likely to be African-American [55]. While different dialysis and demographic factors were analyzed, race was the most significant variable for hypokalemia warranting oral K^+ supplementation [54]. Usually oral supplementation alone is sufficient to correct the deficit. In further analyses, the presence of hypokalemia in PD could not be explained by membrane transport differences, protein intake, concomitant medication or small molecule clearance.

Hyponatremia

Recurrent hyponatremia in anuric infants undergoing PD has been reported. Hyponatremia has been observed especially in infants and young children due to low sodium (Na^+) intake (such as infant formula), renal Na^+ losses, inadequate UF, or obligate Na^+ losses that occur at UF rates necessary to maintain fluid balance in combination with a low-sodium diet. The ratio of Na^+ in the ultrafiltrate to the serum (sieving coefficient) is usually < 1. The initial decrease in dialysate Na^+ during UF indicates Na^+ sieving across the peritoneal barrier. Dialysate Na^+ decreases with 4.25% glucose dialysate, while plasma sodium increases slightly. With very short dwell times utilizing hypertonic glucose, Na^+ removal is lower relative to fluid removal, potentially resulting in hypernatremia. Dialysate sodium may actually decrease during longer dwell periods, suggesting that sodium crosses the peritoneal membrane to a lesser degree than water and more water than sodium is removed in over-hydrated patients.

Adult patients with labile blood glucose, and those on tricyclic antidepressants or clonidine may experience stimulated thirst and increased water intake leading to hyponatremia. Thirst from stimulation of the renin-angiotensin system can also lead to hyponatremia. Notably, the renin-angiotensin system is functioning at a higher level in PD patients than HD patients. Overly rapid correction of acute hyponatremia should be avoided, as it can lead to central pontine myelinosis.

Hypermagnesemia

Hypermagnesemia (1.04 – 1.29 mEq/L) is frequently observed in CAPD patients, and a highly significant inverse relationship exists between immunoreactive PTH and magne-

sium concentrations. The reduction or removal of magnesium from dialysate solution results in normalization of elevated serum magnesium concentration. Decreasing PD solution magnesium concentration from 1 – 1.2 mEq/L to 0.5 mEq/L resulted in clinical hypomagnesemia in 64% of patients, warranting magnesium supplementation. Therefore the concentration of magnesium in the dialysate may be an important determinant for the risk of hypomagnesemia on PD.

Sulfate Clearance

Inorganic sulfate clearance is similar to the clearance of creatinine and phosphate, but significantly less than urea. Sulfate deficits in PD have been reported due to losses in stool, and losses of sulfate in other forms (e.g. taurine, phenol, and sulfate).

Malnutrition

A number of factors are be involved in the development of malnutrition in patients on PD. Anorexia may result from several different factors, including GI tract dysfunction (secondary to DM or medications), and abnormalities in basic metabolic pathways/brain metabolism, either directly or indirectly related to dialysis procedures [48]. However, calories derived from the glucose dialysate load in PD do not suppress appetite as previously believed. Anthropometric and biochemical evidence of protein malnutrition have been observed in 18 (51%) of CAPD patients. Fifty-five percent of PD patients in the CANUSA study were malnourished [69].

Plasma amino acid levels are lower in PD vs. HD patients, although the intracellular amino acid pattern is less abnormal. It is unclear what effect dialysis dose has on amino acid abnormalities. Protein loss in PD is a contributing factor to lower plasma amino acid concentrations. Total amino acid losses over a one-week period average 61.8 ± 14 mM for HD and 38 ± 13 mM for CAPD. Levels of total amino acids, essential amino acids, non-essential amino acids, and branched-chain amino acids were lower in PD than HD.

Because protein-calorie malnutrition is a strong predictor of morbidity and mortality, early intervention utilizing protein supplements or enteral feeding should be undertaken. Amino acid solutions and recombinant human growth hormone (rhGH) have the potential to improve nutritional status of CAPD patients. Insulin may be required to treat hyperglycemia in patients receiving increased glucose loads from a combination of PD and TPN. Malnourished patients on PD receiving parenteral nutrition are at increased risk to develop hypophosphatemia. Phosphate replacement should be supplied cautiously in patients with hypomagnesemia and hypocalcemia due to the risk of bilateral vocal cord paralysis. Severely malnourished patients on CAPD undergoing tube feedings may develop "re-feeding syndrome". This syndrome is associated with clinically significant shifts in P, magnesium, and K^+ from extracellular to intracellular spaces.

Chronically malnourished patients whose cardiac muscle is nutritionally depleted cannot deal with the increase in circulatory demands caused by the initiation of aggressive nutritional support. These individuals may develop acute respiratory distress unless volume is closely controlled. In an earlier report, low-dose intramuscular (IM) nandroline decanoate for ≥ 3 months (100 to 200 mg IM/month) exerted a definite anabolic effect in 9 malnourished PD patients. Megestrol acetate has also been used in PD, both in low- and high-dosages (40 – 800 mg). Its major com-

plications occur with increasing doses: adrenal insufficiency, glucocorticoid deficiency, and thrombosis.

Growth Abnormalities

While children on long-term dialysis experience growth abnormalities, these may occur less frequently on PD than HD, whether or not rhGH is given. Proposed reasons are improved urea control, less acidosis, and caloric support from dialysate glucose. However, protein losses from PD may impair normal growth, especially in infants, and may contribute to permanent loss of growth potential. Recombinant human growth factor-1 (rHuGF-1) and rhGH both have demonstrated beneficial effects on nutritional status in short-term studies. These may be of use in children who demonstrate a decreased ability to grow on PD.

Uncontrolled Diabetes/AGE

Local generation of AGE occurs in the peritoneal membrane. A "washing out" of AGE from the peritoneal membrane takes place after a 12-hour dwell period, when the dialysate concentration of AGE is greater than the plasma concentration. Positive staining for AGE has been documented in the interstitium of the mesothelial layer in the peritoneal membrane. In other studies, there was an observed 200% increase within a 4-hour dwell cycle due to in situ glycation. Peritoneal protein contained a 2 – 4 times greater concentration of AGE pentosidine at all equilibration time points. Dialysis glycolated albumin is linearly related to the glucose concentration of both dialysate and in vitro phosphate-buffered saline. AGE formation, but not glycation, decreased as a function of dwell time, possibly attributable to peritoneal membrane clearance. Transplantation is the best therapeutic modality to normalize both pentosidine albumin linked or pentosamine-free membrane changes.

Worsening blood glucose control can result from the glucose load on PD. Tolbutamide, glipizide, glyburide, and rezulin are oral agents used in controlling hyperglycemia in PD. Further control can be accomplished by the use of IP or subcutaneous (SC) insulin (NPH, regular, 70/30, or 50/50). The mechanism for insulin dosing is different in automated PD than CAPD. Several different techniques for insulin dosing have been proposed. For patients with a life expectancy > 3 years, the target control goals are blood glucose 110 – 160 mg/dL, HbA_1C 7 – 8.5%, and up to 1 – 3 episodes of mild hypoglycemia/week. Magrey et al. [66] reported the correlation of HbA_1C and fasting blood glucose in PD was 2.884 ($p < 0.0001$). Most patients require a sliding scale for optimal control. Blood glucose > 500 mg/dL requires multiple SC doses or IV insulin treatment. A significant percentage of patients on automated PD require SC insulin in addition to IP insulin, whereas those on CAPD can usually be controlled with IP insulin.

Hormonal Abnormalities

Multiple hormonal abnormalities occur in patients on PD [62]. Sexual dysfunction is common in patients on PD, especially in males, and may be related to medications, local disease processes, or systemic disease processes (e.g. DM, vascular or neurologic disease). Patients have decreased testosterone levels and spermatogenesis. An increased fre-

quency of anovulation and low fertility rate in females is related to hormonal imbalances, such as derangements in the positive feedback between estrogen and the hypothalamic gonadotropin secretion. Children may have delays in puberty or central precocious puberty on maintenance PD, the latter being reversible with transplantation. While EPO treatment may improve sexual function, hormonal abnormalities still persist in most patients. Abnormal thyroid function persists on PD with decreased serum triiodothyronine (T3) and total thyroxine (T4), although thyroid-stimulating hormone (TSH) is not elevated. Thyroid-binding globulin, T4, and T3 are lost in the dialysate. Plasma renin and aldosterone are normal or mildly increased in PD. Plasma-18 hydroxycorticosterone is higher and may explain a decreased incidence of hyperkalemia with more incidences of hypokalemia in PD.

Obesity

Weight gain can be a complicating problem on PD. The kilocalorie load from PD is approximately 8 kcal/kg/day, yielding a total daily gain of 35 – 42 kcal/kg/day. This results in a significant weight gain in certain obesity-prone patients. The approach to obesity in PD is problematic. While newer medications have been attempted, their safety and efficacy in renal failure is unproven. Attempts at lowering percent glucose delivered are difficult since energy consumption may be low with inactive individuals.

Neurologic Complications / Psychological Complications

Traditionally a number of neurologic complications can occur in uremic patients on dialysis. Both HD and PD are associated with at least 3 distinct disorders of the central nervous system (CNS): dialysis disequilibrium syndrome, dialysis dementia, and progressive intellectual dysfunction. Specific abnormalities in cerebral metabolism, cognitive changes, psychological abnormalities, neuropathy and autonomic dysfunction can also occur on PD.

Cerebral Metabolism

Cerebral metabolite abnormalities have been identified in patients on dialysis [71]. CAPD patients demonstrate increased choline and myo-inositol levels compared to HD patients. Studies using localized short echo-timed proton magnetic resonance spectroscopy to measure cerebral water and metabolites in humans demonstrated abnormalities consistent with osmotic dysregulation in PD. Abnormal choline/creatinine ratio and N-acetyl aspartate concentration also occur in PD.

While these disorders exist with renal failure, they appear uncorrected by dialysis. Furthermore, the abnormalities affecting the cerebral metabolism are not explained by the effects of specific types of dialysis. More clinically apparent abnormalities, like dialysis encephalopathy in PD, are most likely attributable to impaired response of cerebral osmolites. CAPD may be more effective than HD in reversing uremic encephalopathy by mechanisms unrelated to serum creatinine and urea levels.

Psychological Abnormalities

Both cognitive and psychological abnormalities occur in children and adults on PD. Intriguingly, CAPD patients had consistently better cognitive function than the chronic HD subject group in several studies. A number of tests [50], including the Patient-Related Anxiety Scale (PRAS), Beck's Depression Inventory (BDI), Kupfer-Detre System II Somatic Symptoms Scale (KDS/II) have supported the relationship between abnormalities in psychological status and outcome. Significantly higher complication rates for CAPD patients are correlated with higher scores. Those with the highest scores have more symptoms of depression, anxiety, somatic symptoms and overall poorer quality of life. Fukunishi noted that 65.4% of children demonstrate a separation anxiety disorder or deterioration of psychological adjustment when on home PD [32]. The global intelligence quotient measure by the Wechsler and Bender tests demonstrates that the majority of children have average intelligence (77%), and high verbal IQ, and yet the performance IQ is significantly lower. Less anemia on PD than HD may contribute to PD patients' higher test scores, since anemia adversely affects cognitive performance.

Noncompliance may be observed in a significant percentage of PD patients. The term "noncompliance" represents a complex set of behaviors and interpersonal relationships with family, physician, nurse, and others which has important cultural and ethical considerations. The spectrum of noncompliance can include refusal to accept specific therapeutic recommendations to the most drastic form, which is withdrawal from therapy.

A specific number of psychological factors has been shown to have an impact on compliance in PD patients. These include patients' beliefs about their health behavior, locus of control and self-efficacy, family problems, and social support. However, there is a relationship between compliance and perceived health outcomes in dialysis overall and particularly in PD patients because of their direct involvement in their overall well-being and adequacy of care.

Indices of hyperparathyroidism were significantly associated with headache, joint pain, dyspnea, and nausea. The severity of these somatic complaints seen in patients on PD are connected to the indices of disease-effective disorders and perceived quality of life.

Multiple Neuropathies

A number of different types of neuropathies develop in PD patients, the most dramatic of which is rapidly-evolving inflammatory demyelinating polyneuropathy, also referred to as "pseudo-Guillain-Barré syndrome". The onset of this disorder is from 4 – 10 weeks after beginning PD. This acute or subacute syndrome is characterized by generalized limb weakness developing over days or weeks associated with severe imbalance, diminished reflexes, and numbness. The natural history is significantly different than diabetic or uremic neuropathy. Another form is a more chronic or indolent process, termed chronic inflammatory demyelinating polyneuropathy. Both of these types of polyneuropathy can occur in PD. The mechanism is unclear. Demyelination may result from T cell-mediated destruction of myelin sheaths mediated by tumor necrosis factor (TNF) α, increased immune stimulation and a loss of a myelin-stabilizing factor. The progression of neuropathy may be halted in some cases by significantly increasing the level of middle molecule clearance, although higher doses of dialysis usually do not lead to improvement in symptoms. A reversal of symptoms, or a cessation in symp-

tom progression may occur with transplantation. The above polyneuropathies are characterizes by axonal degeneration with secondary segmental demyelination. Several subclinical disorders of auditory (eighth) nerve function are part of the axonal uremic neuropathy that may occur in patients on PD. This may explain the susceptibility to neurotoxic drugs, including antibiotics.

Peripheral neuropathy can occur in a large number of diabetic patients who have been on PD for > 5 years. Most likely there is some relationship between the adequacy of dialysis and the risk for developing progressive diabetic nephropathy. In diabetes and uremia, the neuropathy tends to be distal, symmetric, sensory more than motor, and involving the lower extremities more than the upper. The development of uremic motor neuropathy is a medical emergency warranting early attention to the dialysis prescription and consideration for combination therapy with either HD or hemodiafiltration (HDF) and PD, to achieve total creatinine clearances per week of > 130 – 150L/wk and/or transplantation prioritization.

A specific type of familial, amyloid polyneuropathy can occur and is characterized by peripheral nerve amyloidosis and sexual dysfunction. Both patients on HD and PD may develop this abnormality.

Autonomic Dysfunction

Autonomic function is significantly reduced in CAPD patients compared to controls [47]. A reduction of sympathetic activity in the limbs and cardiovascular autonomic impairment are seen. Defective regulation of heart rate, due mostly to afferent limb abnormalities, is more common than damage of reflex blood pressure control. There was no difference in the electrophysiological parameters in patients with HD or PD. However, autonomic dysfunction may occur to a greater degree in HD than PD. Impairment of autonomic function in the heart and peripheral circulation may have consequences to overall cardiovascular status, and cardiac dysautonomia may be associated with high incidence of sudden death in both diabetic and uremic patients.

Gastrointestinal Complications

Pancreatitis

The risk for pancreatitis is increased in patients on PD compared to HD, and is a significant cause of increased morbidity in CAPD [15]. Abdominal pain, nausea and vomiting with negative peritoneal cultures or without clinical evidence for peritonitis should suggest the diagnosis of pancreatitis. Contributing factors for pancreatitis include hypertonic dialysate [> 50% of exchanges using 4.25% (3.86%) glucose dialysate], hypercalcemia, malnutrition, gall bladder disease, and time on dialysis > 23 months. An edematous and/or calcified pancreas (Figure 16) on CT is more reliable than pancreatic enzyme elevations. A serum amylase > 3 times the upper limit of normal, or lipase > 4 times the upper limit of normal have a strong correlation with true pancreatitis. The enzyme elevations in HD are higher in the setting of pancreatitis than those that occur on PD. Dialysate amylase is increased to the high normal or above normal range. A dialysate amylase > 100 units/L is suggestive of intra-abdominal pathology, i.e pancreatitis, rather than peritonitis. Serum concentrations of pancreas-specific P3 isoen-

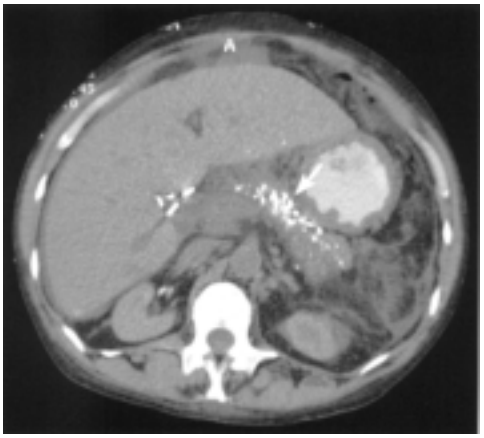


Figure 16. This CT scan demonstrates an edematous calcified pancreas in a CAPD patient presenting with acute pancreatitis.

zyme are increased in approximately 30% of asymptomatic ESRD patients. The treatment of pancreatitis should entail symptomatic care, nasogastric suction, and possible temporary discontinuation of PD.

Motility Abnormalities on PD

Unrecognized gastroparesis may have a critical impact on the morbidity of PD patients. Both diabetic and nondiabetic patients may present with dysmotility and/or delayed emptying while on CAPD. Type 1 diabetics exhibit diabetic gastroparesis more than Type II diabetics (70% vs. 37%) [27]. Patients with longer durations of DM, higher frequency of orthostatic hypertension, history of enteropathy, vascular complications (acute MI, blindness, amputation), malnutrition with DM, poor glycemic control, and a history of increased hospital days with Type 1 diabetes are more likely to have gastroparesis [9]. Eighty-eight percent of patients on PD with gastroenteropathy demonstrate abnormal gastric emptying times. Solid phase label with technetium^{99m} and liquid phase labeled with ^{111}indium are used to diagnose motility abnormalities. Despite abnormal solid emptying, many patients do not suffer symptoms.

Fifty-five percent of PD patients had abnormal carbon^{14} urea breath tests indicative of delayed gastric emptying [63]. Foregut motor dysfunction, and abnormal gastric antral electrical control with gastric dysrhymthia can occur. All CRF patients with anorexoria and vomiting in one study had ≥ 1 disorders of foregut motility. Fasting serum gastrin levels, gastric myoelectrical activity, and bioelectrogastrogram results demonstrated abnormalities, which were not always corrected by dialysis. Clinically, if a CAPD patient has lower esophageal sphincter pressure abnormalities with 2-L dialysis volumes, there is a greater risk for dysmotility symptoms. Thus, the demonstration of an incompetent lower esophageal sphincter pressure may bode poorly for patients wanting to use PD.

Gastric emptying abnormalities in PD are improved with erythromycin elixir or metoclopramide. In one report, gastric emptying time improved from 122 minutes to 12 minutes [24]. Erythromycin inhibits the binding of the GI peptide motilin to its smooth muscle receptor, thus improving symptomotology. Erythromycin doses of 100 mg/2 L administered IP can be given for long-term treatment without apparent side effects. Some reports of tolerance to erythromycin suggest alternating erythromycin (3 weeks) with metoclopramide (1 week).

Malnutrition due to gastroparesis can also occur in nondiabetic patients on PD. Therefore, even nondiabetic patients with persistent decreases in appetite or malnutrition should have radionucleotide gastric emptying scans, both to diagnose gastric abnormalities and to monitor treatment success with promotility drugs. Early satiety or poor appetite in the

absence of nausea and vomiting could also be caused by gastroparesis. Cisapride, while helpful in nonuremic patients with gastroparesis, may contribute to the development of arrhythmias in patients on dialysis and should be avoided.

Gastric Reflux/Bloating

Patients on PD may develop gastroesphageal reflux. Supine lower esophageal sphincter pressure can be checked by esophageal monometry or pH monitoring after instilling 2 L of dialysate. There appears to be no difference in supine vs. sitting positions with respect to lower esophageal sphincter pressure. However, there is an increase in total reflux score (symptomatic reflux, nausea, vomiting, epigastric discomfort) in symptomatic PD patients. Furthermore, the total treatment time wherein the pH was < 4 was significantly greater than anticipated when 24-hour esophageal pH monitoring was utilized.

Non-obstructive Mesenteric Ischemia

Non-obstructive mesenteric ischemia (NOMI) occurs in approximately 30 – 40% of nondialysis patients with mesenteric ischemia or infarction wherein no gross arterial or venous obstruction can be found. NOMI occurs in patients with low cardiac output states from circulatory collapse associated with hypovolemia, cardiac dysfunction, arrhythmias, hypoxia or hemoconcentration (HCT > 41.5). Previous reports have shown that digitalis administration has resulted in preferential mesenteric vasoconstriction in high-risk patients. There have been several reports of NOMI occurring in patients undergoing PD, however the role played by intra-abdominal shunting of blood is unclear.

Ascites

Chylous ascites may complicate PD either soon after starting treatment or in conjunction with an additional surgical procedure. This rare clinical entity is usually secondary to disruption of a lymph channel or lymphoma. The ascites is significantly cloudy or milky, with characteristic laboratory findings of: chylomicrons on lipoprotein electrophoresis, triglyceride levels of dialysate > plasma, and positive Sudan black staining of dialysate supernatant. In 230 cases of chylous ascites in PD patients, malignancy was encountered in only 2 cases. A precise diagnosis was difficult to establish in the remainder. The chylous effusion in 7 cases appeared secondary to sclerosis, chronic pancreatitis, systemic amyloid or cardiac failure; 3 cases were likely due to microtrauma from a Tenckoff catheter. Ascites lasted for > 2 years in 4 cases and required long-term nutritional support. Patients may be able to continue on PD if they are able to maintain a stable nutritional status.

Gastrointestinal Bleeding

GI bleeding is more common in HD than PD patients. Bleeding may result from uremia, iatrogenic causes, underlying systemic disorders, or an unrelated GI disease. Gastritis, duodenitis, amyloidosis, warfarin, increased heparinization, coexistent GI disease, and angiodysplasia are the most common causes for GI bleeding. Angiodysplasia is more common in HD, and is associated with vascular calcifications, constipation and possible chronic venous hypertension. Angiodysplasia should be suspected in patients with

HIV, Karposi's sarcoma, CMV colitis or non-Hodgkins lymphoma. Endoscopy is helpful both in diagnosis and treatment. Erosive gastritis occurs in approximately 30% of dialysis patients with GI bleeding. The remaining cases are due to colonic polyps, esophagitis, melanosis, diverticuli, erosive duodenitis, or gastric ulcer. Patients on PD with intractable vomiting and abdominal pain can present with a gastric ulcer due to *Helicobacter pylori* infection. These patients should be treated with metronidazole, imiprazole, and clarithromycin.

Hepatic Complications

A number of different liver parenchymal diseases may present in dialysis patients including hepatitis C, hepatitis G, and hepatitis B. Both hepatitis B and C are more commonly transmitted through HD than PD, with a risk hazard ratio of 5.7. Biochemical tests are poor indicators of liver disease progression; liver biopsy is indicated as the definitive means of evaluating PD patients with positive hepatitis C viral (HCV) antibodies, as approximately 20 – 25% of HCV RNA carriers in the US develop cirrhosis. The prevalence of anti-HCV among CAPD patients ranges from 1.8 – 15.4%, with 16.4 – 46.7% positivity in HD. Enzyme-linked immunosorbent assay (ELISA) II testing is more sensitive than Recombinant Immunoblot Assay II (RIBA II): positive results in 52% of HD and 14% of PD, vs. 38% HD and 11% of PD patients, respectively [16]. Reports from Singapore demonstrated HCV positivity by polymerase chain reaction (PCR) in 41.5% of HD and 12% of PD patients.

Strict compliance with universal infectious disease precautions from the Center for Disease Control is mandatory for both HD and PD patients. While the duration of PD did not affect risk, transfusion requirements may be a risk factor. HCV infection was observed to be significantly more common in female PD patients; and correlated to events occurring before the start of PD therapy. Therefore, PD should be considered as low risk for HCV infections compared to HD. Increased HCV seropositivity in Ashkenazi Jews points to ethnic factors predisposing to HCV transmission, again with a higher prevalence in patients on HD vs. PD.

The frequency of HCV antibody was significantly higher in hepatitis B-positive patients. Hepatitis B virus (HBV) may not cause significant serum amino transferase elevations in all patients. HBV can be transmitted in the dialysis setting through blood transfusions and environmental surfaces. However, dialysis ultrafiltrate or PD dialysate seems to be an improbable source of HCV dissemination in the dialysis setting. A significant association exists between HBV and the presence of anti-HCV antibodies. Common epidemiologic routes for HCV infection may exist in Hong Kong, China and East Asia. Hepatitis G is a novel RNA virus of the Flavividae family occurring in both HD and PD. The prevalence of HGV infection is similar in HD and PD.

Esophagitis

Esophageal infections can occur especially in diabetic and immunocompromised patients on PD. Diabetic patients, especially those with persistent hyperglycemia, have an increased risk for *Candida*-induced esophagitis, as do alcoholics and elderly patients. Esophageal infections could be due to *Candida*, herpes simplex virus, cytomegalovirus (CMV), and *Mycobacterium tuberculosis*. Dysphagia (difficulty swallowing) and odynophagia (pain on swallowing) may occur, but the lack

of these symptoms should not be used as evidence against esophageal infection. Nausea and vomiting occur in 42% of CMV esophageal infections, whereas weight loss is more common in CMV, tuberculosis (TB), and HIV. Oral lesions are present in 27 – 37% of patients with infectious esophagitis.

The treatment is dictated by the cause and severity of the infection. Nonabsorbable metizole may be helpful. Clotrimazole (nonabsorbable imidazole) 10 mg five times/day, or oral nystatin (nonabsorbable polyene) to disrupt the fungal membrane may also be effective.

Dermatitis Complications

Pruritus

Uremic pruritis affects 50 – 90% of PD and HD patients. Robertson et al. reported the percentage might be somewhat higher in PD vs. HD (61.9% vs. 53.9%) [93]. Pruritis usually starts approximately 6 months after initiation of dialysis therapy. Uremic pruritis may present in either of two distinct patterns: episodic, mild, and localized to the back, dialysis catheter site, face or legs; or generalized and intractable. The actual mechanism for pruritis is unclear. Histologically, there is atrophy both in the sebaceous glands and in the secretory and ductal portions of the eccrine sweat glands. Reduced stratum cornium hydration levels correlate with the degree of pruritis in PD. Usually pruritis occurs in the setting of secondary hyperparathyroidism where divalent ion abnormalities are higher coinciding with iron deficiency and, in some cases, hypervitaminosis A. Specific proteases, leukotrienes, prostaglandin E, and histamine H_2 receptor abnormalities play a role. Theoretically, the higher degree of middle molecule clearance in PD should provide for less pruritis than HD, assuming specific middle molecules play an etiological role in initiating pruritis. While Morton et al. found 27% of HD patients and 54% of PD patients complained of pruritis, other studies have noted no difference in the incidence of pruritis by dialysis modality [74]. Regular emollient use produces a marked reduction in severity of pruritis. Ultraviolet phototherapy may also provide clinical improvement in some patients resistant to standard approaches. Ondansetron (4 mg twice daily PO) may be an effective safe treatment for uremic pruritis in PD.

Calciphylaxis

Calciphylaxis is a disorder characterized by vascular calcification and tissue necrosis. These extremely painful, violacious, and necrotic ulcerative lesions are associated with mottling and gangrene of the extremities (Figure 17). These ulcerative changes can occur over arteries or on the extremities in association with increased PTH, deep Ca skin deposits, and severe hyperparathyroidism especially in DM. Histologic findings may be segmental requiring deep elliptical biopsies to identify Ca deposits. Soft tissue calcifications characterized by tenderness with extensive nonulcerative, large, hard, subcutaneous plaques in the calves and soft tissues may also occur. Bone scanning is positive for Ca deposits, and 75% of the patients have a high Ca-P product.

Other Dermatidites

Recently several patients on PD have developed a hypersensitivity reaction to the glucose polymer, icodextran, characterized by a

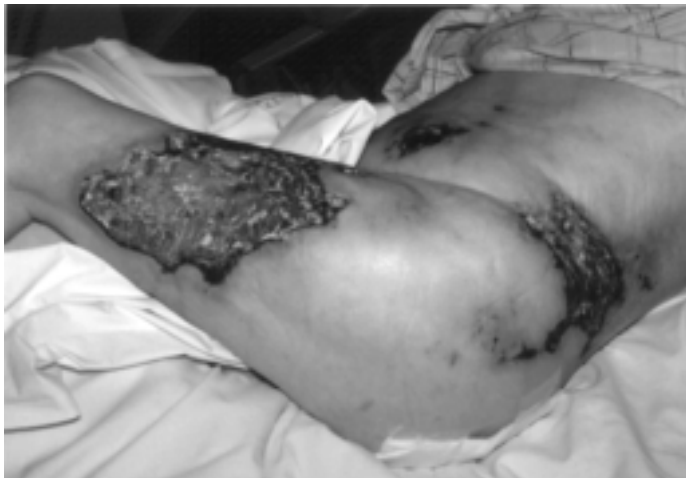


Figure 17. These ulcerative, painful, necrotic lesions in the upper thigh characterized the development of calciphylaxis in this CAPD patient.

pruritic sometimes scaly, exfoliative rash. A case report describing phenytoin toxicity causing secondary porphyria cutanea tarda in PD has been reported.

Hematology/Oncology

Anemia/Red Blood Cell Metabolism

Anemia and complications from its treatment with recombinant human erythropoeitin (rHU-EPO and iron), may occur in patients on PD. While there is an increase in endogenous EPO production in patients on PD compared to HD, the vast majority still require rHU-EPO therapy for anemia. Fifty-five percent of patients on EPO required initiation or an increase in antihypertensive therapy, compared to 19.6% of patients on placebo. Navarro et al. demonstrated in a small group of patients on PD that rHu-EPO requirements necessary to maintain a stable hemoglobin concentration were higher for patients on angiotensin converting enzyme (ACE) inhibitors [76]. The effect of rHu-EPO on peritoneal transport characteristics is unclear. A significant reduction in the levels of protein S and protein C may result from rHu-EPO and could potentially increase thrombotic events.

Dialysate may adversely affect RBC metabolism in PD. Standard dialysate may interfere with the Emden-Meyerhof pathway, the main glucose-utilizing route in the RBC. A damaging action by lactate dialysate on bicarbonate buffering necessary for normal RBC metabolism may occur. High lactate concentrations acutely inhibited the key enzymatic steps of glycolysis, leading to a significant decrease in glucose consumption and adenosine triphosphate (ATP) production. Decreased pH levels observed in lactate-incubated RBC were shown to inhibit observed G-6-PD activity.

Uremia may modulate RBC membrane cation transport, although neither PD nor HD improves this defect. The abnormalities in transport include K^+/chloride co-transport activity, amiloride/Na^+ efflux, and decrease in Na^+-K^+ pump activity.

Peritonitis may inhibit in vitro erythroid colony formation contributing to a worsening in anemia or resistance to rHu-EPO. Seemingly, endogenous pyrogens, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) also inhibit erythyropoiesis. Additionally, a circulating soluable factor inhibiting erythyropoiesis may contribute to the decreased EPO response observed during peritonitis. Iron saturation may be a good indicator of rHu-EPO requirements and responsiveness in PD patients with anemia [49]. Achieving higher iron saturation levels than the currently accepted 20% may further decrease rHu-EPO requirements in PD patients. IV infusion of total dose iron is superior to oral iron in the treatment of anemia in PD, achieving higher HCT (36.0 ± 1.0 vs. 34.4 ± 1.1). Patients on PD who have low iron saturation may develop worsening anemia despite rHu-EPO.

Platelet Abnormalities and Bleeding Diatheses

Patients on PD exhibit a marked increase in the levels of reticulated platelets compared to normal patients. The presence of increased reticulated platelets may indicate platelet hyperreactivity and accelerated platelet turnover; increased platelet turnover is usually associated with uremia [41]. The percent of reticulated platelets in PD vs. normal was 6.96 ± 0.68% vs. 2.77 ± 0.17%; the mean platelet count, however, was normal. The mean percent of reticulated platelets was greatest in HD (8.2 ± 0.36%). There does not appear to be a difference in percent of reticulated platelets between diabetic and nondiabetic patients on PD. The increased turnover rate may contribute to the acquired platelet defect and risk for uremic bleeding. Hypoalbuminemia in CAPD may also play a role although the actual mechanism is unclear.

Abnormalities of platelet surface glycoproteins GPIb and GPIIb/IIIAa (receptors for von Willebrand factor and for fibrinogen) may be involved in uremic bleeding (defect in primary homeostasis) in PD. These values are normalized in PD suggesting better homeostasis and less bleeding if patients are properly dialyzed.

Coagulation Abnormalities

The dialysis procedure can potentially affect both coagulation homeostasis and normal fibrinolysis. Procoagulant markers and fibrinolytic parameters are higher in PD than HD. However, HD increases procoagulant markers significantly over baseline [2]. CAPD patients demonstrate significantly higher levels of factors VII, IX, and X; antithrombin III; protein C; and protein S compared to HD. Furthermore, CAPD patients may have shorter prothrombin times. Enhanced fibrinolysis may be a natural protective mechanism against thrombosis. It is intriguing that a positive correlation exists between abnormalities in hypercoagulability parameters, secondary fibrinolysis, and serum lipids. Patients who demonstrate higher fibrinogen, or higher levels of specific factors in conjunction with abnormalities in lipid metabolism, may have a greater risk for underlying atherosclerosis. This increased risk may contribute to limb ischemia and cardiovascular ischemia.

Mesothelial cells play an important role in determining the fibrinolytic activity of the peritoneum in vivo and may prevent fibrous exudates and fibrin deposition in the peritoneal wall. This function may also decrease adhesion formation. Mesothelial cells express

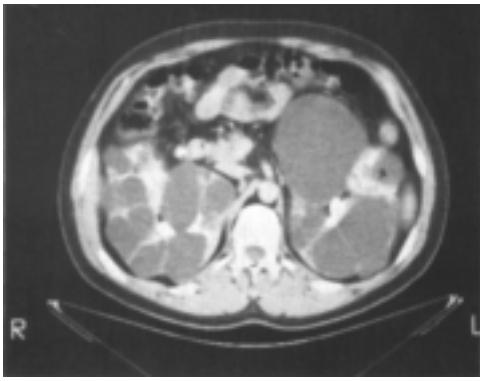


Figure 18. This CT scan demonstrates a renal cell cancer arising from the superior aspect of the left kidney in a patient with polycystic kidney disease on CAPD for five years.

plasminogen activators and inhibitors. Platelets with high PAI levels usually have positive D-dimers. Thus, low D-dimers in the peritoneal dialysate indicate a block in fibrinolysis, and heparin therapy is highly recommended. D-dimer levels may also be able to identify patients who benefit from heparin therapy during peritonitis or increased imbalance between activators and inhibitors in the peritoneal space.

Neoplasia

Speculation has existed for a number of years that uremic patients have an increased risk for malignancies. There are several factors which may increase the risk of cancer in patients on PD, or dialysis in general, including impaired function of the immune system, impaired antioxidant defense mechanisms, accumulation of carcinogenic compounds partly due to impaired renal elimination, and the risk for chronic infection and inflammation. Reports delineating the cancer risk in HD patients are more common, most likely because of the increased numbers of patients on HD worldwide compared to PD. HD patients have a risk of developing malignant tumors that is several times that of the general population. Because both sets of patients are uremic, and uremia itself may have a risk potential for cancer development, PD patients may have a higher risk as well. From 1982 through 1990, 21 urologic cancers were discovered in uremic patients from a single center [60]. Nine of 21 patients were on HD and 1/22 on PD. The standardized incidence ratio of kidney cancer in chronic HD was 24.1 ($p < 0.01$) and that of bladder cancer was 16.4 ($p < 0.01$). Hematuria was the most common presenting feature despite the fact that most patients were anuric. A further study examining the incidence of cancer in a regional dialysis and transplant registry reported a total of 479 cases of cancer, including primary cancers of the liver, kidney, and thyroid; lymphoma; and multiple myeloma [12]. There does appear to be an excess of renal cell and liver carcinomas or lymphomas in patients receiving renal replacement therapy. Acquired renal cystic disease in patients with PKD may progress to renal cell cancer (Figure 18). However, because the numbers still are small, routine cancer screening in ESRD is presently a relatively inefficient allocation of resources. The findings overall highlight the importance of considering a patient's competing risks to survival in designing screening strategies and other interventions targeted to ESRD patients. With reference to PD, specific tumors may, in fact, metastasize to the peritoneum. These include adenocarcinoma of the ovaries, stomach, colon, breast, pancreas, and lung, along with lymphoma and sarcomas. Metastatic cancer is by far the most common peritoneal tumor detected in PD patients.

Transplantation Complications and Immune Defects in PD

Graft Rejection

A number of reports in the literature have examined the difference in graft and patient survival in individuals treated with either HD or PD. Patients on CAPD may in fact have a more normal immune response than HD patients, and this may make them more immunocompetent. To test this theory, several studies have examined graft survival in PD patients who have subsequently undergone renal transplantation. Overall the rate of graft and patient survival appears to be similar between HD and CAPD [23]. The rate of graft loss due to infection may be higher for recipients who were under dialyzed pretransplant irrespective of dialysis modality. Since a significant percentage of PD patients may not achieve target clearances due to loss in residual renal function and inadequate prescription adaption, the potential risk of infection could be increased compared to HD patients. Perez Fontan reported the incidence of acute rejection was similar in both HD and PD, and that PD patients demonstrated lower rates of delayed graft function after renal transplant than a matched control group of patients on HD [84].

Post-transplantation Infection

In pancreas-kidney transplant patients, the incidence of peripancreatic abscess formation was higher in those dialysed pre-transplant with PD than HD (40 vs. 14%), with *S. epidermidis* being the most common pathogen. Douzdjian and Abecassis reported 5% peritonitis and 2.5% CESI rates in PD patients post-transplant [26]. There does not appear to be any difference in nonperitonitis-related infections between HD and PD patients in the postoperative period. Nutritional status, adequacy of dialysis, and time since prior bouts of peritonitis and CESI all have a direct impact.

The risk of developing post-transplant infections linked to the presence of the PD catheter continues to generate concern. In most studies, the persistence of the PD catheter after kidney transplantation has produced no infection or other complications. Catheters can even be safely used during acute rejection or primary graft nonfunction for dialysis. Potentially PD catheters represent an additional source of infection following transplantation if left in place for extended periods of time. Therefore, the catheter may be left in place for the first few weeks following transplantation, however, it should be removed by 3 months after transplantation because of the increased risk of catheter-related infections. Some clinicians suggest removing the catheter at the time of hospital discharge to decrease infection risk.

Renal Allograft Thrombosis

Several studies reported an increased incidence of renal graft thrombosis in CAPD compared to HD patients (7.3 vs. 3.6%) [28, 108]. A more recent study in 827 cadaveric recipients documented vascular thromboses in 4.7% of PD and 6.1% of HD patients, with no difference in the incidence of arterial and venous thrombosis by modality. Graft recipients may require detailed coagulation studies preoperatively to design effective coagulation prophylaxis, especially in cases where allograft harvest will be performed laparoscopically. There appears to be little difference in transplant characteristics, hematologic parameters, immunosuppressive therapy, graft-

ing anatomy, or preservation techniques in those patients who develop renal graft thrombosis. However, several reports associated graft thrombosis with advanced age of donor, use of the right kidney, protracted cold ischemia, delayed graft function, and previous thromboembolic events in the recipient. The presence of anticardiolipin antibodies and certain diseases such as systemic lupus erythematosus (SLE) may be associated with an increased risk of thrombosis.

Post-transplant Ascites

Symptomatic ascites can occur following the discontinuation of PD after transplantation. If the serum to ascites albumin concentration gradient or albumin gradient is > 11 gm/L, some degree of portal hypertension is likely. If the serum albumin gradient is < 11 g/L, then peritonitis, an inflammatory process, or malignancy should be considered. The causes of ascites after transplantation in PD patients include increased net UF pressure in the peritoneal capillaries, increased permeability of the peritoneal membrane to macromolecules, and decreased lymphatic absorption. These are contrasted to the causes of ascites in nonrenal patients, which include fluid overload, functional or structural changes in the peritoneal membrane and lymphatic drainage, heart failure, hypoalbuminemia, pancreatic insufficiency, and hyperparathyroidism. Treatment should be conservative unless malnutrition becomes a predominant factor.

Immune Dysfunction

A profound effect on host cellular defenses occurs in uremic patients and specific dialysis modalities may have an additional adverse effect on these systems. Numerous immunologic complications may occur in PD related to the use of glucose-based dialysate, the development of peritonitis, and/or inadequate solute clearance [44]. In PD patients with peritonitis, both peripheral (systemic) and local (intraperitoneal) immunity are adversely affected. Polymorphonuclear cells (PMNs), lymphocytes, and macrophages undergo abnormal morphologic changes, and show alterations in cellular function and blunted secretory ability. Furthermore, other host defense cells (e.g. mesothelial cells) may experience similar abnormalities of size and function. These changes have an impact on infection rate, time to resolution, and risks for reoccurrence.

Three interrelated mechanisms combine to recruit leukocytes into the peritoneal cavity during periods of inflammation: direct recruitment, bacterial activation of mesothelium, and peritoneal microphage (PMO): human peritoneal mesothelial cells (HPMC) interaction. During peritonitis there is an influx of leukocytes into the peritoneal cavity. An excessive local production of cytokines by HPMC occurs, but is not prognostic for peritonitis or UF failure. Leukocyte recruitment and transmigration across the peritoneal membrane is dependent on the expression of adhesion molecules – intercellular adhesion molecule-1 (IAM-1) and vascular cell adhesion molecule-1 8VCAM-1 – by HPMC. Secretion of IL-6 and IL-8 proinflammatory cytokines synthesized by mesothelial cells is followed by the activation of the lymphocytes then infiltration and the production of T lymphocyte-derived IL-2 and SIL-2R. This normal series of cellular/humoral events is disrupted in PD.

A number of studies have evaluated the selection and differentiation of lymphocytes in the normal peritoneum. In CAPD, T cells may be functionally abnormal and demon-

strate varying levels of T cell activation. Patients on PD have absolute lymphopenia, however overall cellular immunity may be less depressed on PD than HD, as shown by an increase in T cell population after 12 months on PD. Interestingly, peripheral lymphocytes in CAPD patients suffering frequent bouts of peritonitis were characterized by an increased expression of CD44 variant molecules, normally seen with inflammation and malignant disease. CAPD alters normal peritoneal lymphocytes; neither mRNA transcription of the RAG-1 gene nor CD34 cells are detectable in peritoneal cavity lymphocytes in CAPD patients. Also, thymus-independent T cells are undetectable in the peritoneal lymphocytes from CAPD patients. This results in the loss of CD8α+ subset of natural killer (NK) cells (CD3-, CD8αα+, CD16+ and CD56+), which significantly decreases the peritoneal natural killer activity.

Macrophage effectiveness is limited by several factors in PD patients. Macrophage activation via T lymphocytes and NK cells is adversly affected by these cells' abnormalities. Moreover, the macrophages have increasingly immature bactericidal activity due to their constant flow into the peritoneal cavity from the bone marrow. Finally, these immature cells promote inflammation by their increased cytokine generation ability when stimulated.

Mechanisms involved in the abnormal PMN response in uremia include malnutrition, iron overload, intracellular Ca, low and high molecular weight circulating plasma factors, 1,25 dihydroxy vitamin D levels and the dialysis treatment itself. Porter et al. found CAPD corrected the uremic defect in PMN bacterial killing in 22 patients after 3 months on PD [88]. However, there was no correlation to either urea or creatinine levels. A number of granucyte inhibitory proteins have been isolated from the peritoneal dialysate which include granulocyte inhibitory proteins 1 and 2, degranulation inhibiting proteins 1 and 2, chemotaxis-inhibiting protein, and immunoglobulin light chain kappa and lambda. During acute bacterial peritonitis, monocyte chemotactic protein-1 (MCP-1) is the most important monocyte chemoattractant; whereas IL-8, and human melanoma-growth-stimulating activity (huGRO α) are the major neutrophil-attracting chemokines. It is unclear how inadequate PD might affect the synthesis and decreased excretion of these substances. A modified form of ubiquitin, an inhibitor peptide of chemotactic movement of PMN cells in vitro, has also been isolated from PD dialysate. Some studies have shown that PD therapy may restore PMN intracellular hydrogen peroxide generation to normal levels, possibly due to the removal of low molecular weight toxins in CAPD. While hypoalbuminemic CAPD patients (serum albumin < 3.6 g/dL) had significantly depressed superoxide production volume and velocity, there were no observed differences between patients with and without a history of peritonitis. There does not appear to be a correlation between PMN intracellular killing activity and the rate and type of peritonitis. However, patients with impaired PMN bacterial killing are prone to more severe forms of CAPD peritonitis, and possibly to more frequent infections.

Hypogammaglubulinemia has been reported to develop in infants and children on PD. After IP infusion of immunoglobulin (100 mg/kg) in children with peritonitis, chemotaxis of peripheral blood neutrophils increases significantly. Chemotaxis and luminal-dependent chemiluminescence of both peripheral blood and peritoneal neutrophils of children on CAPD treatment were also enhanced with IP immunoglobulin treatment. Low IP levels of IgG in adults may be associated with an increased risk for peritonitis, although other authors found no correlation

between peritoneal fluid IgG and C3 and the incidence of peritonitis. PD patients with hyperparathyroidism may have a resultant inhibitory effect on B cell function.

Dialysate-induced Immune Defects

Several reports have demonstrated the effect of dialysate on cellular and secretory functions in PD. Dialysis fluid may reduce the host's resistance to infection and potentially can affect the rate or severity of infection risk. Alternate fluid formulations have been or are being developed to lessen this effect. Neutral pH solution buffered with bicarbonate or in combination with lactate or glycyl-glycine may be helpful. Glucose polymer dialysate has been associated with a marked depression of cytokine release. Newer solutions containing bicarbonate or pyruvate, rather than lactate, glucose polymers, glycerol or peptides are being developed to avoid potential toxic effects.

Conventional glucose-based peritoneal dialysate leads to depressed oxygen consumption, chemiluminescence, superoxide production, phagocytosis, bacterial killing, and actin polymerization in neutrophils in vitro [51, 52]. Uremic solutes in PD effluent (e.g. p-cresol) in conjunction with glucose depress normal granulocyte NADPH-oxidase dependent radical species production. Impaired adhesion receptor expression and cell adhesion capacity also exist. Dialysate glucose concentration, low pH, and the presence of lactate ions in racemic mixtures containing both the D- and the L-forms may induce cytotoxicity. Glucose plus lactate-based PD dialysate reduces the capacity of leukocytes for chemotaxis, bacterial killing and production of monokines. Standard dialysate solutions may inhibit mesothelial cell proliferation potentially leading to chronic mesothelial cell damage.

Glucose dialysate may adversely affect superoxide generation by both peripheral and peritoneal phagocytes in CAPD patients. The increased superoxide (O2) generation by peritoneal and circulating phagocytes in CAPD patients is at least partly due to the enhancement of hexose monophosphate shunt activity by increasing glucose metabolism and the increased O2 generation might be involved in long-term complications of CAPD.

There has been an individual case of reactivation of SLE after transfer to PD.

Hospitalization Risks and Complication Prevention

Despite increases in the average age of incident ESRD patients from 1996 to 1988 (57 vs. 61 years), the percent of diabetic patients on dialysis (30 – 43%), and the number of co-morbid risk factors, the US dialysis mortality rate has declined to 17%. Hospitalization rates and length of stay have declined but are still unacceptably high. Renal failure patients are 10 times more likely to be hospitalized and on average, hospitalization lasts one day longer compared to non renal failure patients. A national hospital survey identified 348,962 hospitalizations for patients with renal failure in 1991. As the numbers of patients with ESRD on dialysis increase, hospitalizations continue to escalate. Inpatient health resource utilization accounted for 44% of the total cost for the Medicare ESRD program in this study [104]. In 1991 hospital days for ESRD beneficiaries numbered 3.1 million and the total ESRD program expenditures were $2.7 billion.

Haback et al. [37] compared hospitalization for patients treated with PD vs. HD using data

from the USRDS 1993 annual report. Average hospital admission rates/patient-year at risk for PD patients were 14% higher than for those treated with HD after adjustment for race, age, gender and cause of ESRD. Furthermore, diabetic patients treated with PD had a 12% higher admission rate/patient-year at risk than did diabetics treated with HD. Younger diabetic patients (20 – 40 years old) had similar admission rates, whereas patients > 45 years old had an 18% higher admission rate than did diabetics treated with HD. Nondiabetic PD patients had 15% higher admission rates than did nondiabetic HD patients. While this study did not factor in patient co-morbidities from the dialysis modality, the underlying message is that patients with suboptimal clearances despite dialysis have an increased risk for hospitalization and a longer hospital stay. Ten percent of hospitalizations in dialysis patients had a length of stay > 23 days. Children < 5 years old had higher dialysis-related hospitalization rates and durations on PD than HD. Every center should have the ability to track complication rates, at the very least peritonitis and CESI, both in the outpatient and hospital settings.

Providing adequate dialysis is the key not only to survival, but also to avoiding increased hospitalization rates. A recent reexamination of the USRDS data has demonstrated a stable rate of death comparing HD to PD over the last several years, and in some studies, an improved survival rate on PD compared to HD during the first 2 years of therapy. Therefore, complication rates can be decreased by providing adequate dialysis and early preventive intervention in patients who may be at increased risk for complications. Specific risk factors associated with higher rates of hospitalization utilization/year of patient risk include increasing age, decreased activity level defined by a Karnovsky score, DM as a cause of ESRD, and decreased serum albumin level; whereby the strongest predictor of hospitalization rates was low serum albumin level. Every effort needs to be made to modify these and other risk factors.

Diabetic patients had a 40% higher admission rate/patient-year at risk than did nondiabetics. Admission rates were higher for males, whites and PD patients in the Haback study. Excess admission rates among diabetics compared to nondiabetics increased with patient age. PD patients needed 4.6 hospital days/year at risk more than HD patients, with the length of stay averaging 11.74 and 10.58 days/admission for dialysis patients treated with PD and HD, respectively. These findings are modifiable, considering the percent of US patients who require changes in their prescription dialysis to meet target clearances.

Because admission to the hospital significantly increases overall disease morbidity and may result in subsequent increased deaths, avoiding admissions and emergency room visits is of critical importance in dialysis care. In reviewing total hospital admissions by diagnosis [diagnosis-related group (DRG) category for 1993 – 1995], the top 6 systems were circulatory, renal, GI, infection, respiratory and nutrition. Those specifically related to PD include congestive heart failure (CHF), circulatory system, septicemia, nutritional and miscellaneous metabolic disorders, pneumonia, and esophagitis. Understanding these risk factors for hospitalization in ESRD can result in developing interventional strategies to decrease morbidity.

CHF admissions may result from a mismatch between prescription and membrane transport type, often occuring shortly after the initiation of PD. Patients with cardiomyopathy, altered cardiac output, edema at the time of dialysis initiation, and uncontrolled DM may be at increased risk for CHF admissions. Individuals with significant ventricular arrhythmias may also be at increased

risk for compromised cardiac output. Thus, it is essential to optimize diabetic control ($HbA_1C < 8$), achieve euvolemia, and optimize nutrition. Prompt diagnosis of peritonitis with aggressive treatment and identification of limb cellulitis in diabetics is crucial. Nutrition disorders should be vigorously addressed in patients with serum albumin < 3 g/dL. Pneumococcal and influenza vaccinations and early treatment of pulmonary infections may avoid simple pneumonia admissions. Esophagitis may occur in DM, HIV or other immunocompromised patients on PD. Endoscopy may be warranted in patients with persistent nausea, vomiting and poor nutritional status.

On entering PD programs, patients' risk status should be evaluated and pro-active measures taken to avoid hospitalizations. Knowing the level of predialysis glycemic control, an independent predictor of clinical outcome in type II DM, prior to dialysis will aid in risk categorization. Major risk factors in PD include: sepsis, poor nutrition, respiratory dysfunction, esophagitis, peritonitis, uncontrolled DM, LVH, CHF, arrhythmias, CAD, peripheral vascular disease with ischemia, and cellulitis. HIV-infected patients have higher rates of peritonitis. While the risk of nasal *S. aureus* carriage remains controversial, those carrier states identified should be treated (see above). Standardizing treatment approaches and developing care guidelines will help decrease complications warranting admission. Hospitalizations have a negative impact on achieving quality indicator goals; utilizing best demonstrated practices and tracking of patients at higher risk are essential.

By the year 2000, 45 – 55% of all patients on ESRD will have DM as their renal failure etiology. Currently, the major reasons for poor outcome are cardiovascular disease in 56%, cachexia in 18%, and infection in 11%. Impaired vision, decreased manual dexterity, frequent presence of bowel diverticulae, poor hygiene, socioeconomic level, need for caretaker, and impaired immunologic defense all tend to increase with age for patients on PD. The 5-year survival for diabetic patients on dialysis is approximately 18 – 28%. Almost half of all diabetic ESRD patients do not survive 2 years. Peritonitis rates are significantly higher in diabetics vs. nondiabetics. Diabetics have an increased complication risk and a higher hospital admission rate due to coexistent disease. Managing risk is essential to improving this poor outlook.

The drop-out rate from infection is higher in younger patients, whereas elderly patients' increased morbidity and mortality are mainly associated with complications not related to CAPD. Hospitalizations are significantly longer in the elderly, and the risk for malnutrition and decreased muscle mass is higher. There is no difference in peritoneal function, UF rates, peritoneal transport, or clearance goals in young and elderly patients. By the year 2000, 65% of all ESRD patients will be older than 65 years of age. Their special needs will have to be considered: malnutrition, bowel dysfunction, increased chronic diverticulae, DM, neoplasia, peripheral vascular disease, and variable mental alertness which obviously affects self-care.

African-American patients are less likely to be hospitalized, less likely to choose PD as initial therapy (11.6% vs. 29.3%) and are less likely to change dialysis modalities once on HD. African-Americans have an increased susceptibility to *S. aureus* and *S. epidermidis* infections, which should be stressed in preventive strategy initiatives.

Increased peritoneal membrane transport is associated with decreased patient and technique survival for CAPD patients. High-transport CAPD patients have worse nutritional status than those with low-transport characteristics. Potentially, this may be due to

Table 9. In-patient PD Complications Settings[1]

Clinical Settings	Associated Complication	Dialysis Prescription Modifications
Congestive heart failure	– Resistant hypervolemia[2] – Increased a-$A_0$2 gradient – Intubation	– Utilize short dwell times (20 to 60 minutes) – Achieve dry weight ≤ 48 hours – Ultrafiltration (UF) 4% body weight (8 to 10 hours)
Coronary artery bypass grafting	– Reintubation – Sternal infection/osteomyelitis[3] – Hypokalemia – Malnutrition[6]	– Aggressive solute/water removal[4] – Usually automated PD ≥12 hours/day – Achieve preoperative weight
Cellulitis	– Poor infection response – Uncontrolled blood sugar[5] – Persistent limb edema – Amputation	– UF to achieve euvolemia – Remove ALL edema
Aortic-femoral revascularization	– Wound dehiscence, “localized dialysate leak” – Postoperative wound infection[7] – Malnutrition – Resistant edema	– Avoid edema/increase UF – Decrease dwell volume perioperatively – Avoid dialysate “seepage” into wound – Optimize solute clearance
Lower extremity amputation	– Stump dehiscence – Postoperative wound infection – Resistant edema	– BUN/albumin ≤ 17 – optimal fluid removal
Pneumonia	– Resistant infection[6] – Intubation – Sepsis – Interstitial edema – Respiratory failure – Increased A-a0_2 gradient	– Control volume to solute ratio

[1]Design prescription to optimize solute/water removal [vary dwell time days 1 to 3 (i.e., 60, 90, 120 minutes) to establish PET category if previously unknown]. [2]Increased pulmonary capillary wedge pressure (PCWP) > 16 mm water. [3]Avoid chest wall edema to optimize suture-line closures. [4]Achieve BUN/Alb ≤ 17. [5]Optimize blood sugar control, extend perioperative antibiotic prophylaxis. [6]Serum albumin < 3 gm/dL (protein supplements, entero feedings, total parenteral nutrition, megastrol acetate 40 Ä 400 mg daily). [7]Utilize IV antibiotics, aggressive pulmonary toilet.

increased losses of protein in the dialysate and volume expansion attributable to decreased UF. High-transport patients have lower serum albumin concentrations even at one month into CAPD and the serum albumin remains lower at 2 years on CAPD.

A number of inpatient clinical settings further increase the risk for PD-related complications (Table 9): CHF, cellulitis or sepsis, acute MI, ischemic heart disease or unstable angina. Recovery following laparoscopic cholecystectomy, coronary revascularization,

amputation, heart valve surgery, recent extubation are all considered as compounding high risk transition periods for patients on PD. Specific parameters should be followed in these patients, and glucose control, dialysis prescriptions, and nutritional support adjusted to meet the ongoing demands. It is essential that the clinician anticipate problems and structure care to prevent problems from developing in high-risk clinical settings.

Patients admitted to the hospital should have special attention given to effective solute removal and volume control. These patients may need significantly longer times on automated therapy, particularly if they are hypercatabolic. Ideally, the BUN to albumin ratio should decrease ≤ 17 through aggressive dialysis. Patients with serum albumin levels < 3 g/dL should undergo enteral feedings or aggressive oral supplementation. Patients are not compliant in taking daily protein supplements in the hospital for a multitude of reasons and therefore, enteral feeding is preferable. Total parenteral nutrition may be utilized if the GI tract is not functional. Volume control is especially important in patients postoperatively, especially those who have limb surgery. Edema in a limb or in the inguinal area may increase the risk for wound dehiscence and secondary bacterial infection. Aggressive UF should occur to decrease peripheral edema and maintain effective respiratory status. Dialysis patients (especially diabetics) have a significantly higher rate of reintubation than standard individuals.

Impaired pulmonary oxygenation in diabetic patients undergoing coronary artery bypass grafting (CABG) can be a worrisome problem because of various structural and/or functional abnormalities of the lung in diabetics [96]. Pulmonary diffusion capacity and pulmonary capillary blood volume are compromised in patients with diabetes perioperatively. The pulmonary capillary wedge pressure is the variable that has the greatest effect on pulmonary function in the nondiabetic group. Low FIO_2 and high central venous pressure are indicators of pulmonary compromise. The alveolar arterial oxygen (A-aPO_2) gradient and respiratory index are more abnormal postoperatively in diabetics than nondiabetics at similar volume levels. Therefore, smaller elevations above normal in wedge pressure or central venous pressure above normal in a diabetic patient may significantly increase the risk for pulmonary failure and need for reintubation. Effective UF in maintaining low capillary wedge pressure is essential to optimizing the A-aPO_2 gradient.

Impaired ventilatory response to carbon dioxide in CRF patients has grave implications in the intensive care unit. Optimally-dialyzed PD patients demonstrate definite improvement in the ventilatory response to CO_2. CRF patients have a poorly-responsive ventilatory control system, which makes them more difficult to wean from mechanical ventilation, making them even more vulnerable to disturbances in blood gas homeostasis and subsequent respiratory arrest. Reintubation adds significant risk to overall mortality perioperatively.

Summary

ESRD patients treated with PD have the potential to develop serious complications across a broad spectrum of organ systems. While many complications are directly related to dialysis itself, a number are due to the uremic state unaffected by the specific dialytic modality. Because of the overall risk for CRF patients on dialysis to undergo hospitalization, steps taken to avoid admission are

crucial. High-risk patient groups have been identified and warrant closer follow up in the outpatient setting. Specific medical problems which increase the risk of hospitalization should be aggressively treated. Patients admitted either emergently or electively should be closely followed in the hospital, and aggressive dialysis for solute and water removal implemented along with supplemental nutritional support if indicated. Preventive strategies both in the outpatient and inpatient arenas can significantly decrease morbidity and optimize overall long-term survival.

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Anemia of Chronic Renal Failure

William J. Stone

Historical Background

In 1836 Richard Bright first commented on the pallor of patients with poor kidney function. The combination of pale mucous membranes and yellow-brown skin, sometimes darker on the face, may lead the examining physician to suspect the diagnosis of chronic renal failure (CRF). As documented by Erslev and others [1, 2], the degree of anemia is approximately proportional to the level of renal dysfunction as measured by blood urea nitrogen (BUN), serum creatinine, or creatinine clearance (Ccr). The worse the glomerular filtration rate (GFR), the lower the hematocrit (HCT) will be (Table 1). A plot of HCT versus serum creatinine is shown in Figure 1. When renal function is < 15% of normal, the HCT is almost always in the 20's. In the study of Hakim and Lazarus, the mean HCT for patients with a serum creatinine of 5 – 10 mg/dL was 29%, and for those with a serum creatinine > 10 mg/dL, it was 26% [3]. The HCT rarely falls < 20% due to uremia alone. If such a patient is encountered, other causes of anemia, such as iron deficiency, microangiopathic hemolysis, or multiple myeloma as a cause of chronic renal failure (CRF), should be sought.

Table 1. Equations Relating Renal Function and Hematocrit

HCT = –2.1 serum creatinine + 44, p < 0.001 (both sexes)
HCT = –2.52 serum creatinine + 45.9, p < 0.0001 (men)
HCT = –1.36 serum creatinine + 37.7, p < 0.0001 (women)
HCT = 0.48 Ccr – 0.0031 $(Ccr)^2$ + 26.0, p < 0.0001 (men)
HCT = 0.48 Ccr – 0.0031 $(Ccr)^2$ + 21.5, p < 0.0001 (women)

HCT = hematocrit (%), serum creatinine (mg/dL), Ccr = creatinine clearance (mL/min), Data taken from reference [2]

Physiology of Erythropoiesis

In 1950 Reissman showed that the hypoxic rat caused enhanced erythropoiesis in its parabiotic, non-hypoxic partner [4]. Then Erslev in 1953 demonstrated a hormone in anemic animals which stimulated erythropoiesis when injected into non-anemic recipients [5]. This factor did not affect white blood cells or platelets. Four years later Jacobson and colleagues reported that the kidneys must play a key role in the release of this hormone, erythropoietin (EPO) [6]. It then became accepted that the kidneys sense an oxygen deficit and respond by increasing EPO production. Under normal conditions, a plasma EPO

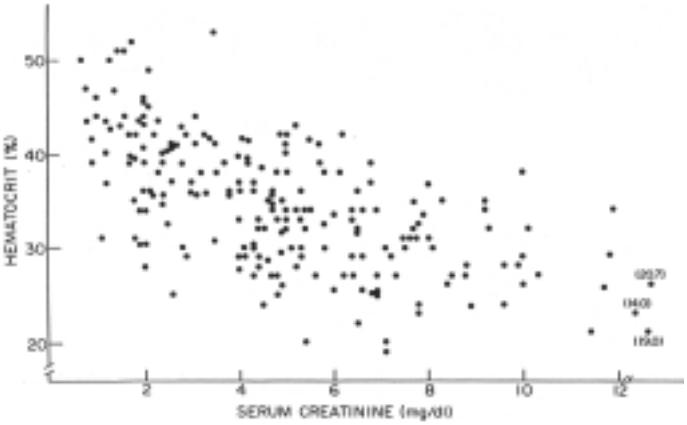

Figure 1. Concentrations of serum creatinine and hematocrits of individual patients from the Nashville Department of Veterans Affairs Medical Center (VA) Renal Clinic are plotted.

level of 8 – 18 mu/mL will maintain a baseline rate of erythrocyte synthesis, an adequate oxygen delivery to the kidneys, and thereby continued EPO synthesis [7]. In severe anemia (HCT < 20%) the plasma level of EPO may increase as much as 100-fold in an attempt to restore the erythrocyte mass to normal. Thus there is a hormonal feedback loop involving the kidneys which controls erythrocyte production.

In 1977 Miyake et al. purified EPO from human urine (from patients with aplastic anemia) [8]. However, the use of EPO as a therapeutic agent was severely hampered by the small quantities which could be extracted. By 1985 the human EPO gene had been isolated, cloned, and expressed in mammalian cell lines by 2 groups [9, 10]. Biologically active human EPO could now be produced in large quantities.

EPO is a heavily glycosylated protein consisting of a single strand of 165 amino acids with an equal amount of carbohydrates. Its molecular weight is 30,500 daltons [7]. The gene coding for EPO is found on human chromosome 7 and consists of 5 exons and 4 introns. A downstream enhancer is sensitive to hypoxia. An hypoxia-inducible factor (HIF-1) binds to this enhancer and acts as a transcription factor [7].

Koury et al. first demonstrated that EPO messenger RNA (mRNA) was localized to a small fraction of renal cortical interstitial cells near the base of proximal tubular cells [11]. The rate of EPO production correlated not only with HCT but also with the number of renal interstitial cells expressing EPO mRNA. In mild anemia EPO positive cells are present in small groups in the inner cortex. In maximum anemia (HCT < 15%), cells throughout the cortex possess EPO mRNA but still compose only 7% of the total interstitial cells. The mechanism by which this recruitment occurs is unknown.

EPO can also be produced by hepatocytes and other non-renal tissues in small quantities. However, this supply of EPO to the body is inadequate to restore normal hematopoiesis in the absence of normal renal parenchyma.

The erythrocyte progenitor cells which are the main targets for EPO are the mature burst-forming units-erythroid (BFU-Es) and colony-forming units-erythroid (CFU-Es) [7]. The EPO receptor on these cells is a 55,000 dalton member of the cytokine receptor superfamily. In the absence of EPO, these cells undergo apoptosis. In the presence of adequate quantities of EPO, CFU-Es are transformed into erythroblasts, then to reticulocytes, and finally to mature erythrocytes. Thus

the effect of EPO is not one of enhancing the proliferation of erythrocyte precursors, but rather of inhibiting apoptosis of these same cells.

Causes of Anemia Related to Chronic Renal Failure (CRF)

Anemia begins to be manifest when renal function (Ccr) is < 40% of normal, approximately when the serum creatinine is above 2 – 3 mg/dL. The erythrocytes of patients with CRF are normocytic and normochromic. Reticulocytes are diminished for the degree of anemia. Iron, folate and vitamin B_{12} stores are usually normal.

Decreased erythrocyte survival in the uremic state has been documented by 3 techniques: ^{51}Cr or ^{14}C-cyanate tagged red cells or by carbon monoxide exhalation [12]. In general, the hemolysis is mild and red cell survival is approximately 50% of normal. Erythrocytes transfused into uremic patients have a similarly shortened life span, while uremic red cells survive for a normal period when transfused into normal subjects [13]. Therefore, the cause of this hemolysis is deemed to be extracorpuscular. Neither maintenance hemodialysis nor chronic peritoneal dialysis (PD) improves red cell survival. However, this form of hemolysis is not a major reason for the anemia of CRF since a normal kidney-marrow feedback system would easily compensate for it.

There is also evidence that the uremic state inhibits production of erythroid stem cells and their offspring [13]. Among the purported inhibitors accumulating in uremic serum are spermine, spermidine and parathyroid hormone (PTH). Uremic animals have been shown by some investigators to have a subnormal response to exogenous EPO. Pharmacologic doses of EPO are sometimes required in dialysis-dependent anemic humans. Other studies have been unable to document any inhibition of erythropoiesis in CRF. Marrow inhibition is at best of minor significance in the pathogenesis of uremic anemia.

The most important cause of anemia in CRF patients is a deficient production of EPO in response to diminished renal oxygen delivery [7, 12, 13]. Serum levels of EPO are much less in uremia than in other types of anemia where there is normal renal function. As long as the kidneys were not surgically removed, a stable HCT in the 20's could be maintained in patients during the era prior to EPO therapy. Following total nephrectomy, all dialysis patients became transfusion-dependent. In our experience, an average of 2 units of red cell transfusions were required per month to maintain the HCT at 20% in anephric patients. Nothing else worked. Androgens had no effect. Iron was not indicated since iron stores were either normal or increased in anephrics. Before EPO therapy, only a successful renal transplant could correct transfusion-dependent anemia in an anephric patient.

Aggravating Factors

Problems that decrease the response of the marrow to endogenous or exogenous EPO can worsen uremic anemia (Table 2). Proinflammatory cytokines such tumor necrosis factor α (TNFα), and interleukins 1 and 6 (IL-1, IL-6) inhibit the effect of EPO on the bone marrow [7]. This may occur in inflammatory

Table 2. Causes of Anemia Related to Chronic Renal Failure

A. Primary Causes
1. Underproduction of EPO
2. Shortened erythrocyte survival due to uremia
3. Inhibitors of erythropoiesis accumulating in uremia

B. Aggravating Causes
1. Factors hampering EPO production or effect*
   a. Inflammatory states
   b. Infections
   c. Nephrectomy
   d. Aluminum accumulation
   e. Neoplasia
   f. ACE inhibitors
2. Deficiency states
   a. Iron
   b. Folate/B_{12}
   c. Malnutrition
3. Other hemolytic states
   a. Oxidant drugs/toxins
   b. Microangiopathic hemolysis (e.g. accompanying malignant hypertension)
   c. Hypersplenism
   d. Dialysis-related factors (hypotonic dialysate, hyperthermia, copper loading,etc.)
4. Hemorrhage/blood loss
   a. GI Tract (platelet defects may contribute)
   b. Dialysis-related blood losses
      (1) During vascular access puncture and needle removal
      (2) Into dialyzer and blood lines
      (3) For laboratory tests
5. Diseases causing both anemia and renal failure
   a. Sickle hemoglobinopathies
   b. Scleroderma
   c. Systemic Lupus Erythematosus
   d. Lead intoxication
   e.Paraprotein disorders
6. Hyperparathyroidism

*See Table 4 about factors causing rHu-EPO resistance

states (e.g. rheumatoid arthritis), during infections, or with malignant neoplasms. Although aluminum accumulation has decreased as a problem in CRF patients lately because of better purification of dialysate water and less use of aluminum-containing phosphate binders, aluminum overload can cause EPO resistance or total insensitivity. The mechanism may involve an interference with iron metabolism. Following the advent of EPO therapy, iron deficiency has become a major therapeutic challenge. This will be covered later in this chapter. Either vitamin B_{12} or folate deficiency may occasionally contribute to defective erythropoiesis in CRF patients, but both are rare due to dietary counsel and multivitamin supplements.

Hemodialysis is accompanied by a peculiar set of problems, some of which were never seen before dialysis became widespread. Hemolysis may be caused by overheated dialysate (51°C) and by hypotonic dialysate when concentrate is allowed to run out. Contamination of dialysate with chloramines, copper, zinc, formaldehyde or sodium hypochlorite (bleach) may also cause hemolysis. Hemolysis due to shearing of red cells has been seen when dialyzer blood is pumped at high speeds through small needles or cannulas. Treatment with hemodialysis leads to massive whole blood losses but in small increments. It has been estimated that with each hemodialysis 15 – 25 mL of blood is lost into the dialyzer, on to the gauze pads used to control bleeding and in the blood lines despite careful rinsing. This blood loss is further aggravated by blood withdrawn for laboratory tests. When summed over the typical 156 dialyses each patient receives every year, over 3 L of whole blood have been removed. It is no wonder that iron deficiency is rampant in dialysis units.

Of minor importance are the following factors. GI bleeding from gastritis, duodenitis,

peptic ulcers or colonic lesions may be enhanced by heparin used during hemodialysis or by uremic platelet dysfunction. The latter is almost never a problem by itself. Drugs may contribute to hemolysis if they are oxidants or blunt the response to EPO (angiotensin-converting enzyme (ACE) inhibitors). Hypersplenism and hyperparathyroidism rarely contribute to uremic anemia. One final category, which is sometimes forgotten by clinicians, concerns diseases which cause both renal failure and anemia, but not necessarily by the aforementioned mechanisms. Among these are sickle hemoglobinopathies, lead intoxication, systemic lupus erythematosus (SLE), scleroderma, and paraproteinemias such as multiple myeloma. In these diseases, anemia out of proportion to the level of renal dysfunction may be a clue to the correct diagnosis.

Table 3. Therapy of Uremic Anemia in the Pre-EPO Era

1. Correction of nutritional deficits
   a. Iron
   b. Folate - vitamin B_{12}
   c. Protein-calorie
2. Provision of adequate dialysis
3. Androgens
4. Avoidance of total nephrectomy
5. Red cell transfusions
6. Rarely indicated
   a. Splenectomy
   b. Parathyroidectomy

Therapy of Uremic Anemia in the Pre-EPO Era

Maintenance hemodialysis became available in many centers in the U. S. in the late 1960's. Widespread use of hemodialysis followed over the next 20 years. Initially, most dialysis patients were young and had disease limited to the kidneys (glomerulonephritis, polycystic kidney disease (PKD)). Individuals with systemic illnesses, such as diabetes mellitus (DM), were usually not dialyzed. Hemodialysis was employed as a temporizing measure until the patient could receive a renal allograft. A large percentage of maintenance hemodialysis patients were able to be transplanted in the late 1960's and early 1970's. Transplantation corrected uremic anemia and occasionally was accompanied by erythrocytosis.

Anemia was considered to be a minor part of the uremic syndrome in these young patients. Levels of HCT in the 13 – 19% range were tolerated if the patient was receiving all available therapy (short of transfusion) and if the patient could function at that low HCT. Red cell transfusions were withheld because of the risk of sensitization to future allografts and the risk of viral hepatitis. However, red cell transfusions were still widely used out of necessity for very low HCT values, for acute blood loss or for symptoms attributable to anemia which could not be corrected by less toxic therapies. As dialysis practice widened in the 1970's and early 1980's, older and sicker patients were being dialyzed. Very low levels of HCT could not be tolerated by these patients, and transfusion usage increased.

Standard therapy of anemia began with the provision of adequate protein-calorie nutrition, folate, vitamin B_{12}, and iron (Table 3). Both of these vitamins were known to be dialyzable. The usual criteria for iron deficiency in non-uremic subjects (serum iron, total iron binding capacity, and ferritin) were

found to be too stringent when applied to dialysis patients, resulting in a change in the guidelines toward higher values. For example, a serum ferritin of less than 20 ng/mL would be indicative of iron deficiency in a normal subject, whereas a value of 100 ng/mL might be too low in a dialysis patient.

Most patients were hemodialyzed for 4 hours on cellulosic dialyzers using blood flows of 200 – 250 mL/min and dialysate flow of 500 mL/min. This would be substandard in many patients by today's ideas of dialysis adequacy. However, it was typical to see an increase in HCT averaging about 5 points in the first few months following dialysis initiation if the patient was not anephric. Some patients, typically those with PKD, normalized their HCT levels with dialysis, iron and vitamins alone. Those few patients who had to be totally nephrectomized and thus lacked endogenous EPO could not be managed this way and had to be regularly transfused.

Another helpful adjunct to uremic anemia therapy at that time was the use of androgens [14]. Androgens somehow augment the efficacy of EPO. Therefore, androgens do not work in anephric patients unless EPO is supplemented. Although both oral and parenteral forms of synthetic androgens were used in some dialysis units, we found them to be too toxic to the liver. Testosterone enanthate (1 – 4 mg/kg) as a once weekly injection had few side effects and would increase the HCT by up to 5 points in the average patient with native kidneys intact. However, the response was slow and not all patients were helped. In our center in the late 1970's, the mean HCT was 26% in 30 "nephric" patients receiving testosterone and an average of 0.1 units of packed red cells per month (very few patients were transfused). The mean HCT in surgically anephric patients (N = 6) was 20%, and they received an average of 2.1 units of packed red cells per month.

Although rarely indicated and controversial in success rate, both splenectomy and parathyroidectomy have been advocated as helpful in certain patients. In the former, excessive erythrocyte destruction by the spleen should be carefully documented prior to surgery. Reversal of increased marrow fibrosis is cited as the reason for the effect of parathyroidectomy on uremic anemia. We have not seen it in our patient population.

The EPO Era

Introduction

Since deficiency of EPO is the major factor in uremic anemia, provision of EPO to affected patients would be the ideal treatment. After the EPO gene was cloned in 1985, it was transfected into Chinese hamster ovary (CHO) cells enabling the production of EPO in large quantities [10]. The purified protein is immunologically and biologically identical to human urinary EPO. It is prepared for administration to patients in a buffered saline solution containing 0.25% human serum albumin. Vials (1 mL) of 2000, 3000, 4000 and 10,000 U/mL are available.

Clinical Trials

In late 1986 and early 1987 the first studies of the use of recombinant human EPO (rHuEPO) on a large scale (10 dialysis patients in the U. K. and 25 dialysis patients in the U. S.) were published [15, 16]. Almost all patients responded with an increase in HCT, a cessa-

tion of need for blood transfusions, and a general improvement in the sense of well-being and exercise tolerance. In the U. S. study, intravenous doses of 1.5, 5.0, 15, 50, 150, and 500 U/kg body weight of rHu-EPO were given thrice weekly at the end of dialysis. Baseline HCTs were 19 – 22%. At the 1.5 and 5.0 U doses, no changes in reticulocytes or HCT were observed. Beginning at 15 U/kg thrice weekly, there was a dose response affecting both maximum HCT and the rate of rise of HCT. At 15 U/kg thrice weekly a HCT of 24% was achieved in 12 weeks; at 50 U/kg thrice weekly the HCT rose to 40% in 11 weeks; and at 500 U/kg thrice weekly the HCT normalized to 42% in 6 weeks. Seventeen patients wound up receiving 25 – 100 U/kg thrice weekly as maintenance therapy for 3 – 7 months in order to maintain HCTs of 35 – 40%. The adverse effects were minimal, chiefly exacerbation of hypertension in 24% and hyperkalemia. Hyperkalemia occurred because 2 patients felt so much better that they saw no need to continue a renal failure diet.

These phase I – II trials were followed by a phase III study involving 333 U. S. hemodialysis patients beginning in the fall of 1986 [17]. All had a HCT < 30%. rHu-EPO in a dose of 300 U/kg thrice weekly was given intravenously to the initial patients. This dose was lowered to 150 U/kg thrice weekly shortly after the study began. Once a target HCT of 35% was achieved, the rHu-EPO dose was adjusted to a maintenance dose required to keep the HCT at 32 – 38%. The response rate was 97.4%. An elevated reticulocyte count occurred in the first 2 weeks, and an increased HCT was seen within 2 – 6 weeks. Erythrocyte transfusions were eliminated in all patients within 2 months of starting rHu-EPO. The median maintenance rHu-EPO dose was 75 U/kg thrice weekly. Adverse effects included iron deficiency (43%), exacerbation or new appearance of hypertension (35%), seizures (5.4%), and myalgias (5%). The rate of vascular access clotting was no different (0.5 clotting events/patient/year) than in dialysis patients not receiving rHu-EPO. No patient developed antibodies to rHu-EPO. The 9 patients out of 333 who failed rHu-EPO therapy had other reasons for anemia including myelofibrosis, chronic infection, and hemorrhage.

Taking everything into account, the results of this large and expensive undertaking were overwhelmingly positive. Nearly all patients could normalize their HCTs, whether or not they had residual renal tissue. Improvements in the quality of life were remarkable. The drug was not only effective, if iron stores were maintained, but was also safe. The main thing to look out for was the exacerbation of hypertension.

rHu-EPO Pharmacokinetics and Dosing

Similar to other parenteral medications, subcutaneous (SC) dosing of rHu-EPO is followed by lower peaks and higher troughs than with intravenous (IV) administration. Following an IV dose, there is rapid disappearance ($t^{1/2}$ = 6.8 hours), and low rHu-EPO concentrations are seen at 24 – 48 hours [18]. With subcutaneous (sc) administration, therapeutic levels may be seen for 72 – 96 hours. As little as 40 U/kg thrice weekly or 60 U/kg twice weekly of SC rHu-EPO can maintain plasma EPO levels within the probable therapeutic range (30 – 100 mu/mL) (see Figure 2). Thrice weekly intravenous (IV) doses of 40 U/kg result in subtherapeutic EPO concentrations during a significant portion of the time. Therefore, there is a greater economy with the SC route of administration. On the average, 25 – 40% less rHu-EPO is required during SC

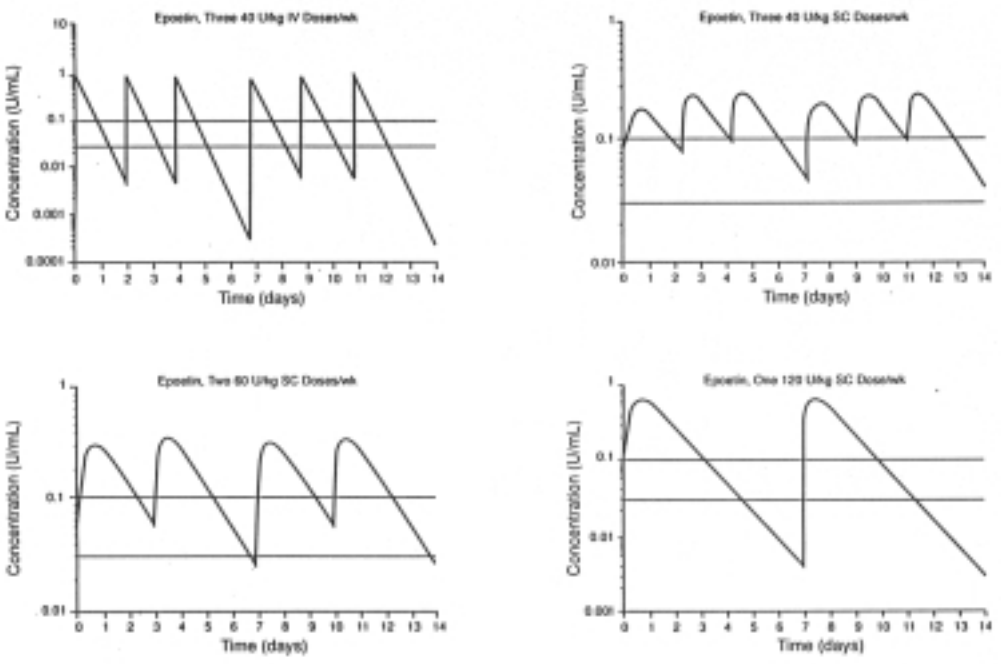

Figure 2. Concentration time simulations for differing strategies at a constant erythropoietin dose of 120 U/kg/week. With permission from Besarab et al. [18].

compared to IV dosing to obtain the same effect. The rate of rise in HCT (points/week) is linearly related to the logarithm of the rHu-EPO dose (U/kg thrice weekly). The steepest part of the curve, and therefore the most efficient incremental response, oc curs between a dose of 40 and 150 U/kg thrice weekly (Figure 3). Above a dose of 150 U/kg thrice weekly the increase in HCT is less steep.

Patients should be replete in iron, folate, and vitamin B_{12} before commencing rHu-EPO therapy. Percent transferrin saturation (TSAT) is the most cost-effective test [19]. The initial recommended dose is 50 – 100 U/kg thrice weekly, either SC (preferably) or IV. We round off to the nearest 1000 U. If after 6 weeks, the patient's HCT has not increased by 5 – 6 points or the desired HCT of approximately 35% has not been achieved, then the dose may be increased in increments of 25%

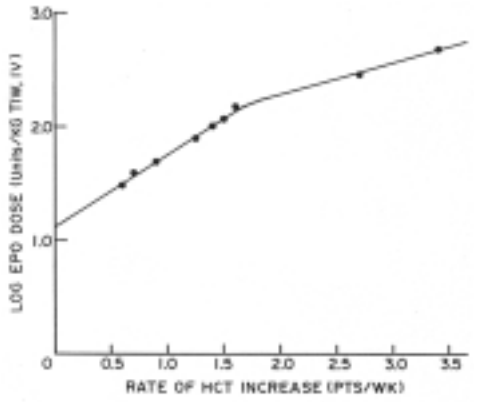

Figure 3. The logarithm of the rHu-EPO dose is plotted against the rate of increase of HCT. Note the change in slope above a dose of 150 U/kg IV 3 times per week (log = 2.18). Data are replotted from reference [25].

of the maintenance dose or 25 U/kg. An interval of 4 weeks should elapse between any dose adjustment thereafter since the erythropoietic response may not maximize for 2 – 6 weeks. If the HCT exceeds 36%, rHu-EPO should not be discontinued since this shuts off erythropoiesis. We prefer to decrease the rHu-EPO dose by 25%. Again, the time to equilibrate with the new lower dose will be 2 – 6 weeks.

Intraperitoneal (IP) administration of rHu-EPO has been tried in chronic PD patients. The response is hampered by the slow peritoneal transport of proteins of this molecular weight (30,500 daltons) into the circulation which may take more than 12 hours. The patient, of course, also needs to be dialyzed. In our opinion IP rHu-EPO should only be used as a last resort after the failure of SC dosing. IP administration should be in a small volume (40 mL) injected into the dry peritoneal cavity followed by a 10 mL saline flush [20]. Overnight undialyzed dwell times approaching 12 hours would lead to maximum absorption and potential TIW dosing in quantities similar to the SC route. When SC rHu-EPO dosing is used in PD or CCPD patients, they require less rHu-EPO on average than hemodialysis patients. Although the cause of this difference is unclear, potential reasons include less iron deficiency, blood losses, and laboratory testing than in hemodialysis patients.

rHu-EPO Resistance

Some patients require large doses of rHu-EPO (≥ 300 U/kg thrice weekly) to restore erythropoiesis, or do not respond at all. Table 4 lists most of the common reasons for this resistance [21]. However, it is not always possible to find the cause in an individual refractory patient. A careful search for iron deficiency in either an initially refractory patient or in one who becomes unresponsive during maintenance rHu-EPO therapy is a good starting point.

Table 4. Causes of rHu-EPO Resistance

1. Iron deficiency
2. Inflammatory states a. Infections b. Rheumatoid arthritis and other connective tissue diseases
3. Inadequate dialysis
4. Deficiency of folate/vitamin B_{12}
5. Aluminum toxicity
6. Marrow fibrosis due to hyperparathyroidism
7. Hemolysis
8. Hemorrhage
9. Hemoglobinopathy
10. Anemia of chronic disease
11.Drug interactions and toxicities

There is no perfect test of iron stores in a patient with CRF. A serum ferritin concentration < 50 ng/mL almost always reflects iron depletion, and a value of < 100 ng/mL may indicate deficiency. Ferritin is an acute phase reactant and may be elevated in the face of low iron stores if there is concomitant infection, inflammation, liver disease or neoplasia. The per cent transferrin saturation (TSAT) may be a useful adjunct to the ferritin. A value < 20% usually indicates iron depletion. In 52 patients with a HCT less than 25% during rHu-EPO therapy, 60% had a serum ferritin < 100 ng/mL, a TSAT < 20% or both [22]. Many of these patients had been prescribed oral iron tablets. Others use a TSAT cutoff of < 25% to define an iron-responsive group of anemic

dialysis patients [23] (See Figure 4). Recent data from Wave 1 of the Dialysis Morbidity and Mortality Study (USRDS 1996) suggest that despite use of rHu-EPO in over 80 – 90% of dialysis patients, 48% had a HCT < 30% [54]. A total of 54% had TSAT < 20%; almost 25% had TSAT < 10%; and 36% had serum ferritin < 100 ng/mL. These data suggest that iron deficiency partly explains the failure to reach the target HCT of > 30%.

Most hemodialysis patients and some PD patients will require oral iron to maximize the response to rHu-EPO (see Table 5 for a list of oral iron preparations). Table 6 lists helpful hints to assure compliance with oral iron therapy. Patients must be educated that iron deficiency is the most common cause of a suboptimal response to oral iron therapy. Attempts to give iron on an empty stomach have generally failed in our hands due to GI side effects. Medications that decrease gastric acidity (e.g. cimetidine), phytates (green, leafy vegetables) and tannates (tea, coffee, red wine) may also diminish iron absorption.

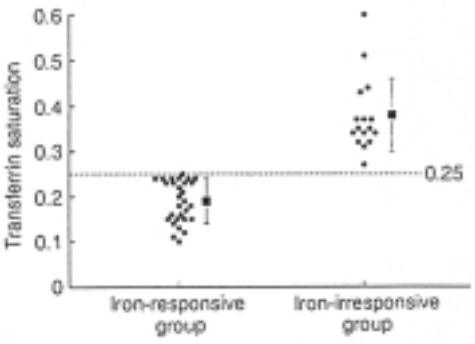

Figure 4. Serum transferrin saturation cut-off value between iron-responsive and iron-unresponsive anemic dialysis patients. With permission from Tarng et al. [23]

Some patients will be noncompliant with oral iron (suggested dose: ≥ 200 mg of elemental iron/day), and this will blunt their responsiveness to rHu-EPO. Other patients will be unable to replete iron stores (e. g. a serum ferritin > 100 ng/mL) on oral therapy [25]. Parenteral iron dextran is a key option in these groups. It is formulated in 2 mL ampules containing 50 mg of iron/mL. We give 100 mg into the venous line over 5 minutes at the end of dialysis. Ten doses are given over 10 dialyses for a total of 1000 mg per course. A course may be repeated if indications of iron deficiency persist. For home hemodialysis (HD)

Table 5. Oral Iron Preparations

Preparation	Trade Name	Elemental Iron/Tablet	Daily Dose (To supply 200 mg elemental iron) Total
Ferrous sulfate	Feosol	65 mg	TID (195 mg)
Ferrous fumarate	Tabron	100 mg	BID (200 mg)
Ferrous fumarate	Chromagen	66 mg	TID (198 mg)
Iron-polysaccharide complex	Niferex-150	150 mg	one tab Nif-150
	Niferex W/C	50 mg	Plus one tab Nif. W/C=200 mg
	Niferex elixir	100 mg/5 mL	5 mL BID=200 mg

Table 6. Factors Aiding Compliance with Oral Iron. Preparations and Maximizing Intake of Iron

1. Patient education
2. Increased dosage per day
   a. Smaller, more frequent doses
   b. Bedtime doses
3. Administration by dialysis nurses of at least 2 doses per hemodialysis
4. Alternative iron formulations for variety and less GI side effects
5. Pharmacy monitoring of refills
6. High iron food
7. Separation of the ingestion of phosphate binders from the time of oral iron dosing; e. g. iron before meals and binders after meals

and PD patients with absolute iron deficiency, 1g of iron dextran (in 500 mL saline) or 500 mg (in 250 mL saline) can be administered in the home training unit after a test dose of 25 mg iron. A test dose of 0.5 mL (25 mg of iron) is given before each course followed by observation to avert anaphylactoid reactions or anaphylaxis. However, even test doses can cause anaphylactoid reactions in 1% of patients and result in 40% of all anaphylactoid reactions [26]. The incidence of anaphylaxis is about 1 in 1000 doses, so dialysis units must be prepared to handle such an emergency. Adverse reactions occur in about 5% of patients, but most are not serious [26]. An acute large joint arthritis can be caused by the iron dextran itself. Itching and wheezing are the most common adverse events.

Chronic low doses (25 – 200 mg/week) of parenteral iron dextran have been given routinely to hemodialysis patients in the U. S. and Europe as an alternative to oral iron therapy [27]. Benefits have included an increase in mean HCT, a decrease in rHu-EPO dose by 33 – 46%, and an overall cost savings. The potential risk of iron overload when such doses are given over a long period of time has not been assessed. Another factor in need of study is the use of supplemental androgen therapy to decrease the rHu-EPO dose and resultant expense.

rHu-EPO resistance may also be caused by undiagnosed or untreated infections. Our first patient with rHu-EPO resistance had a staphylococcal diskitis and vertebral osteomyelitis. His neck pain was attributed to osteoarthritis, which was also present, and there was no fever or leukocytosis. rHu-EPO resistance led to a search for a reason and to the correct diagnosis. Patients with active non-infectious inflammatory states such as rheumatoid arthritis may require higher doses of rHu-EPO. Other reasons for rHu-EPO resistance are summarized in Table 4. Folate deficiency may develop in HD patients who either restrict their protein intake (because dialysis loss of folate exceeds dietary intake), or who require phenytoin therapy. The presence of red cell macrocytosis suggests folate deficiency, if iron overload is excluded. Oral folic acid therapy corrects or prevents this complication. However, most dialysis patients ingest enough dietary folate to remain in positive folate balance.

Benefits of rHu-EPO

Quality of Life

Almost everyone involved in the initial rHu-EPO studies has an anecdote to tell about this subjective variable. One of my patients, a 42 year old farmer, was forced to sell his hogs and cattle when he went on dialysis because of poor exercise tolerance. He required 4 units of packed red cells per month to maintain a HCT of 20 – 22%. Within a few months of his participating in the Phase III rHu-EPO trial,

he had a HCT of 35 – 38% and needed no transfusions. He was able to go back to full-time farming, a rigorous occupation.

Beusterien and colleagues studied 484 dialysis patients who had not been previously treated with rHu-EPO [28]. All patients were assessed by 6 scales taken from the Medical Outcomes Study 36-Item Health Survey at baseline and 49 – 180 days later. Despite a rise in HCT from only 25.5 to 29.9% at follow-up, significant improvements occurred in physical and social functioning, vitality, health status, mental health, and mental component summary score. Activity items showing better scores were looking after the home, social life, interests/hobbies, and sexual satisfaction. The amount of change in HCT was a significant predictor of quality-of-life improvements. Others have reported increases in energy and activity levels, functional ability, appetite, taste for food, cold tolerance, and sexual function. Sleep patterns have also improved in patients receiving rHu-EPO with less insomnia at night and fewer naps during the day.

Cardiorespiratory Benefits

MacDougall et al. studied 10 hemodialysis patients by maximum exercise testing, pulmonary function tests, echocardiography, chest roentgenography, and rheological assessment over 12 months as they initiated rHu-EPO therapy [29]. After 2 months of rHu-EPO, significant increases in exercise time, maximum oxygen consumption, and anaerobic threshold were seen. There was a substantial decrease in exercise-induced cardiac ischemia and left ventricular mass (by echocardiography and chest roentgenogram). Other hemodynamic changes seen in rHu-EPO-treated patients are increased venous tone, peripheral vascular resistance (PVR), blood viscosity and tissue oxygenation [25]. Decreased left ventricular end-diastolic diameter and left atrial diameter have accompanied the diminished left ventricular mass. Overall, there is improved ventricular performance due to increased oxygen delivery. Hemodialysis-related hypotension is less of a problem in rHu-EPO-treated patients.

Reduction in Transfusions

Prior to rHu-EPO therapy, approximately 50% of hemodialysis patients were transfused each year [30]. A mean of 10 units was given annually to each transfused patient. The risks of this practice include hypersensitivity reactions, viral hepatitis, human immunodeficiency virus (HIV), sensitization to HLA antigens, iron overload, and a variety of less common complications. Following a response to rHu-EPO therapy, the need for transfusions is nearly abolished. In the U. S. Phase III trial, 333 patients had received 1030 units of red cells in the 6 months prior to starting rHu-EPO therapy [17]. During the next year, only rare patients were transfused for blood losses at surgery or for medical complications. By avoiding blood transfusions, the rHu-EPO-treated dialysis patient is a better candidate to receive a renal transplant because of less viral hepatitis and lower amounts of panel-reactive HLA antibodies.

Enhanced Cerebral Function

Poor cognitive function is a part of the uremic syndrome and is helped by the initiation of an adequate maintenance dialysis regimen. rHu-EPO therapy has shown measurable benefits even above adequate dialysis. Grimm et al. found objective improvement in several tests of brain function following rHu-EPO therapy [31]. As the HCT increased from 22.7

to 30.6%, auditory event-related potentials and multimodality stimulus-related evoked potentials improved. Marsh and colleagues also found improvement in event related potentials and 4 neuropsychological tests following 3 – 12 months of rHu-EPO therapy [32]. During this investigation, HCT values increased from 23.7 to 36.5%. Thus, improvement in anemia was directly linked to better cerebral function.

Miscellaneous

Although standard blood coagulation tests such as prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen concentration are unchanged following treatment with rHu-EPO, mild increases in platelet count and platelet aggregation as well as decreased bleeding time have been observed [25]. The higher HCT may force more platelets toward the periphery of blood vessels and promote hemostasis in response to injury.

Immune function has benefited from rHu-EPO therapy in 3 areas: phagocytosis/chemotaxis, antibody responses to vaccines, and cell-mediated immunity [25]. Some of these changes may be related to a better nutritional status.

Adverse Effects of rHu-EPO

Hypertension

During the first 3 months of the U. S. Phase III trial of rHu-EPO, 35% of patients developed an increase in diastolic blood pressure of ≥ 10 mm Hg or needed increased doses of antihypertensive medications [17]. Subsequent multicenter studies in Europe, West Germany, and Japan have demonstrated a similar incidence. This phenomenon has not been seen in normal subjects, HIV positive patients, patients with advanced multiple myeloma, or rheumatoid arthritics with normal renal function treated with rHu-EPO. Risk factors for the development of rHu-EPO-induced hypertension besides CRF are high rHu-EPO dosage, IV administration, rapid correction of anemia and severe anemia before rHu-EPO therapy (HCT < 20%). Postulated mechanisms include increased blood viscosity, loss of hypoxic vasodilatation, heightened endothelin production with imbalance of local endothelial factors – endothelium derived relaxing factor (EDRF) and endothelin 1 –, and increased free calcium in vascular smooth muscle cells. In practical terms, the development of hypertension post-rHu-EPO can be prevented or ameliorated by achieving good control of blood pressure prior to beginning therapy via medication and by maintaining low interdialytic weight gains. Blood pressure should be monitored not only during dialysis but also on non-dialysis days. Adjustments in fluid weight and dosages of antihypertensive drugs are almost always able to prevent serious hypertension in rHu-EPO-treated patients. This is especially important in the first two months of therapy. With this approach, there is no difference in severe hypertension (diastolic pressure > 110 mm Hg) in rHu-EPO-treated vs. control subjects [7].

Iron Deficiency

Careful monitoring of iron stores in all patients receiving rHu-EPO is mandatory. During the Phase III rHu-EPO trial, 43% of patients became iron deficient despite oral iron [17]. Serum ferritin and TSAT values should be obtained monthly during the 3 month initiation phase and then at least quarterly thereafter. If the patient is receiving parenteral iron,

the tests should be drawn 2 – 4 weeks after the last dose of iron dextran since false elevations are seen before that time.

Seizures

Seizures were seen in the Phase I – II rHu-EPO trials and were attributable to hypertensive encephalopathy in nearly all cases [15, 16]. Patients had a prodrome of headache and visual blurring. Unlike hypertensive encephalopathy, papilledema is often absent. In Phase III of the U.S. multicenter study, seizures were reported in 5.4% of patients receiving rHu-EPO. This was not significantly different from the incidence (4 – 6%) in the control dialysis-dependent population [17]. Although there is no evidence suggesting rHu-EPO is epileptogenic, uncontrolled hypertension resulting in changes in cerebral perfusion is undoubtedly a major factor. Good blood pressure control as in the Canadian Multi-centre Trial has resulted in no excess appearance of seizures in the rHu-EPO-treated group versus controls. Therefore, seizures can be avoided during rHu-EPO therapy by careful attention to the maintenance of normal blood pressures by medication and avoidance of hypervolemia.

Vascular Access Clotting

Hemodialysis patients regularly clot their vascular accesses, especially if they are synthetic – polytetrafluoroethylene graft (PTFE). Native arteriovenous fistulas are less at risk. Although a control group was not included in the U.S. Phase III trial, the incidence of access thrombosis seen (0.5 events per patient year) was similar to non-treated patients [17]. Subsequent investigations have shown a higher incidence (up to 3-fold) of PTFE fistula clotting in rHu-EPO-treated versus control patients. This is not a reason to withhold rHu-EPO therapy. Patients who appear to have this problem can be managed with careful attention to vascular access performance (venous pressure, recirculation) and intervention by radiologists or surgeons prior to complete thrombosis. Antiplatelet drugs may be a helpful adjunct. Sreedhara et al. found dipyridamole to be beneficial in patients with new PTFE grafts [33]. However, aspirin did not improve the risk of thrombosis in these grafts. Neither dipyridamole nor aspirin had any beneficial effects in patients with prior thrombosis of PTFE grafts. Dialyzer clotting has been successfully managed by modest increases in heparin dosages.

Less Efficient Hemodialysis

This was a theoretical problem because higher HCT values would result in a smaller plasma volumes. Most studies saw either small or no changes in BUN, serum creatinine, serum potassium, and serum phosphate following initiation of rHu-EPO therapy. The few instances of severe hyperkalemia were more related to dietary indiscretions than to inefficient hemodialysis. In this era of frequent monitoring of dialysis adequacy by urea kinetics, any loss of dialysis efficiency due to rHu-EPO will be measurable and can be compensated for by alterations in dialysis parameters, such as blood flow and type of dialyzer employed.

Summary

Monitoring for adverse effects of rHu-EPO should be done on a routine basis in all treated patients. Attention to achieving normal blood pressures and adequate iron stores is of para-

mount importance. Fistulas need to be monitored for signs of impending thrombosis such as increased percent recirculation and higher venous pressures (VDP). Decreased hemodialysis access flow as measured by duplex ultrasonography has been shown to be a significant predictor of future HD access thrombosis and may be a more promising technique compared to VDP monitoring. Dialysis adequacy (urea reduction ratio > 70% or *Kt/V* > 1.4) should be measured on a regular basis, and the dialysis prescription adjusted accordingly. Fortunately, antibodies to rHu-EPO continue to be an extremely rare occurrence.

Table 7. Indications for rHu-EPO in Pre-dialysis Patients with Anemia

1. Left ventricular hypertrophy
2. Coronary artery disease
3. Upcoming elective major surgery
4. HIV nephropathy
5. Students
6. Job holders and at-home mothers with small children
7. Transfusion dependence
8. Living-related transplant candidates

rHu-EPO in the Pre-dialysis Patient

Pre-dialysis patients (Ccr of 10 – 30 mL/min) with HCT values < 30% are candidates for rHu-EPO therapy. Similar guidelines are followed as in dialysis patients. Blood pressure must be normalized and iron stores replenished prior to starting rHu-EPO therapy and monitored during treatment. Initial studies using 50, 100, or 150 U/kg IV thrice weekly have shown good response rates and few adverse events [34]. Target HCTs were 33 – 36%. Progression of renal insufficiency was not increased by receiving rHu-EPO, in the setting of blood pressure control and avoidance of rapid increases in Hct (> 4% increase in 4 weeks). Subsequently, others have demonstrated efficacious use of SC rHu-EPO in doses of 75 – 150 U/kg thrice weekly or even 75 – 150 U/kg once weekly [35]. Patients in whom predialysis rHu-EPO is particularly recommended are listed in Table 7.

A beneficial aspect of predialysis rHu-EPO is its potential for reducing left ventricular hypertrophy (LVH). The adverse effects of LVH are well documented in the dialysis population including the relative risk of death that it confers [36]. Furthermore, once established, LVH rarely regresses in dialysis patients. Levin and colleagues recently noted that the prevalence of LVH in a predialysis population was 38.9%, and this percentage increased with progressive renal failure [37]. LVH was present in 26.7%, 30.8%, and 45.2% of patients with Ccr > 50 mL/min, 25 – 49 mL/min, and < 25 mL/min, respectively. Logistic regression analysis revealed that age, Ccr, hemoglobin, and systolic blood pressure were significantly different between those patients with and without LVH. The last two, as modifiable risk factors, could potentially be controlled to lessen the consequences of LVH in the dialysis population.

rHu-EPO and Renal Transplantation

A successful renal transplant results in a peak serum EPO level of 100 mu/mL or more within the first week after grafting even if the

patient is still oliguric [38]. This is followed by a falling serum EPO concentration as graft excretory function improves. A second EPO peak is seen from day 20 to day 50. HCT values return to normal range in the first 1 – 2 months, and serum EPO levels are normal by 2 months postgrafting. About 10 – 15% of renal transplant recipients develop erythrocytosis (HCT > 51%), usually within the first 2 years [39]. Factors other than EPO may be involved, and the condition rarely spontaneously resolves. Therapy consists of phlebotomy, ACE inhibitors, and consideration for native nephrectomy.

It is controversial as to whether and when rHu-EPO therapy should cease in a dialysis patient who receives a renal allograft. Because endogenous EPO production picks up rapidly in non-rejecting renal transplants, prudence would dictate that rHu-EPO therapy be stopped either at the time of grafting or within the first 2 weeks thereafter. Most episodes of acute rejection are brief enough not to require reinstitution of rHu-EPO. However, in the chronically failing allograft, anemia will recur in a similar manner as in native kidney failure. If patients with chronic renal insufficiency from graft disease or rejection become anemic, rHu-EPO therapy should be resumed following guidelines similar to those for predialysis patients.

Conclusions

The past 10 years have seen a revolutionary treatment of the anemia of CRF evolve and gain broad acceptance. rHu-EPO therapy has been remarkably effective in correcting anemia and returning most patients to a better state of health. With careful management few adverse events are observed. The overall benefits to patients are almost as great as those of maintenance dialysis itself. While recognizing this remarkable progress, it is not sufficient to stop there.

As of late 1995 in the U.S., 90% of hemodialysis patients and 60% of peritoneal dialysis patients were receiving rHu-EPO therapy. The mean HCT was 31.4%, and the median HCT was 32% [40]. At a minimum cost of $10 per 1000 units and a mean dose of 5000 units thrice weekly, $7800 would be spent per patient per year on just rHu-EPO. It is not unreasonable to assume that 200,000 CRF patients in the U.S. are now being treated with rHu-EPO for an overall annual cost of $ 1.56 billion. These figures only consider the expense of rHu-EPO itself. The development of a cheaper method of treating the anemia of CRF is of paramount importance. Areas of clinical research which may help alleviate the problem somewhat include determining the optimum HCT range with the lowest risk to benefit ratio, finding the best method of achieving and maintaining normal iron stores in the presence of rHu-EPO therapy, and the optimization of rHu-EPO-sparing adjuncts such as androgens. Patient and physician education programs still have a long way to go. SC administration of rHu-EPO is not being used enough. In 1993, 92.5% of rHu-EPO doses were given IV and only 7.5% were SC [24]. Since SC rHu-EPO is about 40% more effective, switching IV to SC dosing could result in a large cost saving. Finally, new laboratory investigations may provide cheaper, small molecular weight peptide mimetics of rHu-EPO [41]. Such molecules have been discovered and may possibly be developed into pharmaceuticals. Competition may also lower the price of the established drug.

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Dialysis Prescription and Adequacy

Thomas A. Depner

Background

When dialysis was first used to treat acute renal failure in the 1940's, its overwhelming success in reversing the dreaded and commonly fatal uremic syndrome supported the concept that uremia results from a toxic effect of accumulated solutes that are normally excreted by the kidneys [38]. Equally impressive results in the 1960's when dialysis was first used to treat end-stage renal failure (ESRD), confirmed this impression [59]. Thousands of people who previously had no hope of survival have extended their lives with this modality that has come to be regarded, with the passage of time and accumulation of experience, less as a treatment and more as a preventative measure. Using this preemptive approach to prevent uremic intoxication, dialysis caregivers seek to sustain near-normal quality of life for people with ESRD. The treatment plan, which includes measuring the effect of dialysis and comparing the measurement with established standards, would be easy to monitor if the major toxins responsible for the uremic syndrome were known and could be measured. Unfortunately, despite many decades of research, no single toxin or group of toxins has been pinpointed as the cause of one or more of the symptoms and/or signs of uremia. Instead clinicians are limited to measuring serum concentrations of familiar small solutes, like urea and creatinine, that are known to depend on native renal function for elimination but have little inherent toxicity. Because they accumulate rapidly to relatively high levels and dialyze easily, these familiar compounds are better measures of the dialysis process itself than of uremic intoxication.

In contrast to their heavy reliance on urea and creatinine levels in patients with progressive renal failure prior to reaching end-stage, nephrologists have found that serum levels of these compounds fail to provide a reliable index of dialysis adequacy. Instead, careful prospective investigations of morbidity and mortality, such as the United States National Cooperative Dialysis Study (NCDS), have underscored the importance of providing a minimum dose of dialysis regardless of solute concentrations in the patient [42, 30]. The dose of dialysis is expressed as a clearance, adjusted to the patient's size, of the same small molecular weight compounds (urea and creatinine) that were used with poor success in the past as markers of uremic toxicity. Minimum standards have been established for HD treatments administered 3 times per week and for continuous peritoneal dialysis (PD) [20, 21]. With respect to small solute removal, the extracorporeal synthetic membranes used for hemodialysis (HD) are presumed to function in a manner closely parallel to that of the native visceral and parietal peritoneal membrane. The following paragraphs describe the rationale and methods for quantfying, prescribing, and assessing the adequacy of both HD and PD.

Molecular Basis of Uremic Toxicity

Uremic Toxins

A wide variety of solutes that accumulate in patients with advanced renal failure are shown in Table 1 along with their respective molecular weights. The smaller solutes diffuse easily across the semipermeable dialysis membrane and are effectively removed by dialysis while some of the larger compounds are not removed at all. Some may be removed in part by adsorption to the membrane and some of the larger compounds may be removed more effectively by high flux (high porosity) membranes. Some of the compounds listed in Table 1 cause symptoms similar to those observed in uremic patients (e.g. the guanidines) but only when levels in the serum are much higher than observed in patients with overt uremia.

Alternative Theories

It is difficult to imagine that despite all the sophisticated methods of chemical separation and identification available today, and the numbers of patients available for investigation that the critical toxins have not been identified. Although existence of an elusive but dialyzable toxin remains possible, the failures of the past has spawned alternative theories to explain uremic toxicity. Many of these theories have fallen into disfavor because they fail to account for the dramatic and life sustaining effect of dialysis, which offers little more than removal of relatively small solutes and water from the blood. An attractive alternative explanation and perhaps the reason that a single toxin cannot be identified is that uremia rep-

Table 1. Compounds Known to Accumulate in Renal Failure*

Suspected Uremic Toxins	Molecular Weight
Nitrogenous end products of protein metabolism	
Urea	60
Creatinine	113
Guanidines	
Methylguanidine	73
Guanidinoacetic acid	117
Guanidinosuccinic acid	175
Others	
Peptides and proteins	
β-2 microglobulin	11,800
End products of nucleic acid metabolism	
Uric acid	168
cAMP	240
Pyrimidines	100 – 200
Condensation products of carbohydrate metabolism	
Glycosylated proteins and Amadori products	
Pentosidine	
Phenols and phenolic acids	100 – 300
Indoles	200 – 400
Furans	200
Amines	
Aliphatic (e.g. dimethylamine)	46
Aromatic (e.g. hippuric acid)	179
Polyamines (e.g. spermine)	202
Inorganic elements and compounds	
H^+	1
H_2O	18
Na^+	23
Al^{3+}	27
Mg^{2+}	24
K^+	39
Ca^{2+}	40
PO_4^{3-}	95
SO_4^{2-}	96
Others	
Hormones	
Parathyroid hormone	9500
Renin	40,000
“Natriuretic hormone”	?

*modified from reference [15] with permission from Kluwer Academic Publishers

resents the summation of multiple small sublethal effects of the solutes listed in Table 1.This theory is actually not new, as it was proposed by Homer Smith in his textbook, *The Kidney*, in 1951:

"The retention of urea itself, however, does not account for the toxic manifestations and physiological disturbances of renal failure, and the actual cause of death must be conceived as complex and possibly representing the summated action of numerous physiological disturbances, no one of which may be lethal itself and no one of which is consistently predominate in the uremic state."

Homer Smith, *The Kidney*, 1951, p 854 [61]

Accumulating evidence also suggests that the illness we call "uremia" is complex, consisting of an immediate life-threatening accumulation of small solutes, a more indolent effect of less readily dialyzed solutes, and several indirect phenomena such as the hormone deficiencies that cause anemia and bone disease [9, 25]. Included in the latter category are carbamylation of proteins due to the effects of cyanate which is predictably associated with high urea concentrations (Figure 1), and a maladaptive effect of uremic acidosis that increases protein and amino acid degradation and contributes to the loss of lean body mass [49, 50]. Since protein catabolism is an acidifiying process, the accumulation of acid has potential for inciting a vicious cycle where protein catabolism causes acid accumulation which leads to more protein catabolism. Like other isolated effects of uremia, however, accumulation of acid cannot be considered fundamental to the uremic syndrome because correction of acidosis alone is not enough to reverse it.

Regardless of the pathogenesis, the effects of uremia appear to reverse almost completely with dialysis or transplantation, especially if the renal failure is treated early. After prolonged kidney failure, irreversible effects appear such as infertility and vascular disease. Accumulating evidence also suggests that malnutrition may not be reversible, especially in older patients, if intervention with dialysis is delayed [53].

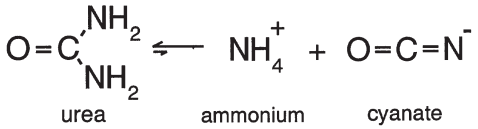

Figure 1. Urea in solution equilibrates with small amounts of cyanate. The reaction is shifted far to the left.

Surrogate Toxins: Urea and Creatinine

Enthusiasm for quantifying the severity of uremia by measuring the level of accumulated solutes has been tempered somewhat by data showing that reliance on available solute levels, such as urea and creatinine concentrations, as the sole determinant of dialysis success or failure, can be misleading and may endanger the patient. As mentioned above, serum levels are determined both by native kidney and dialyzer function and by the generation rates of each solute, which are often variable and dependent on other factors that do not correlate with the severity of uremia. Failure to include the generation rate when interpreting the level can lead to false conclusions regarding the risks of uremic intoxication and adequacy of dialysis.

Urea

Similar to the guanidines, high concentrations of urea can be associated with uremic-like symptoms such as bleeding and gastroin-

testinal disturbance, but only at concentrations above the usual clinically encountered levels [5, 36, 47, 64]. Urea stands in the center stage of the *toxic-solute/dialysis-adequacy* controversy, but its popularity has undergone wide-amplitude fluctuations over the past 3 decades. The original concept of urea as a toxin that heralded a patient's impending risk of uremia was dashed by studies in the late 1960's and early 1970's in patients with both acute and chronic renal failure, in which urea was added to the dialysate to prevent its removal by HD. The patients experienced symptomatic and objective improvement despite no change or an actual increase in serum urea concentrations [36, 47]. Following this discovery, the spotlight was turned to hypothetical "middle molecules" that were thought to mediate the uremic syndrome, but removal by dialysis was limited by their somewhat larger (middle) molecular size that decreased transport across standard dialysis membranes [4, 60]. The NCDS, however, showed that levels of urea and presumably other small solutes correlated much more strongly with patient morbidity than the time spent on dialysis, the surrogate for middle molecule removal [42] in that study. Further analyses of the NCDS data showed that the dose of dialysis correlated better than serum urea levels with outcome [30] and suggested that reliance on the urea concentration as an indicator of need for dialysis could lead to a downward spiraling vicious cycle as shown in Figure 2.

Nephrologists continue to measure urea levels in ESRD patients but the levels are used to estimate the effective small solute clearance rather than as a marker for uremia in both HD and PD patients. Guaranteeing a minimum small solute clearance is the currently accepted best method to minimize uremic complications, effectively insuring the adequacy of dialysis. Once the clearance is measured, the absolute level of urea in the serum is used as a measure of protein nitrogen appearance from which the patient's protein catabolic rate (PCR) can be calculated (see discussion below of PCRn).

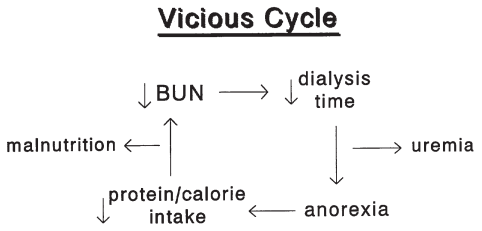

Figure 2. A potentially vicious cycle was uncovered from analysis of the NCDS data. A fall in the BUN, for reasons other than improvement in renal or dialysis function, may lead to a false sense of security as other more toxic solutes are retained.

Creatinine

The serum creatinine level is used as an index of declining renal function in patients prior to end-stage but has not proven useful for this purpose in dialyzed patients [55]. On the contrary, mortality has been correlated inversely with creatinine levels, presumably because malnutrition-related reductions in muscle mass are stronger determinants of mortality (Figure 3). Muscle mass may decline due to uremia-associated anorexia, but the fall may also be related to declining health from other comorbid conditions such as heart failure or infection [43, 52]. Although not useful in this context, serum creatinine levels are easily measured and could be used to assess effective dialyzer clearance in place of urea clearance as outlined above. However, creatinine is less diffusible than urea, develops larger concentration gradients both within the patient and across the dialyzer, and is slower to re-equilibrate when dialysis ceases. These properties of creatinine introduce more error into the measurement of dialyzer clear-

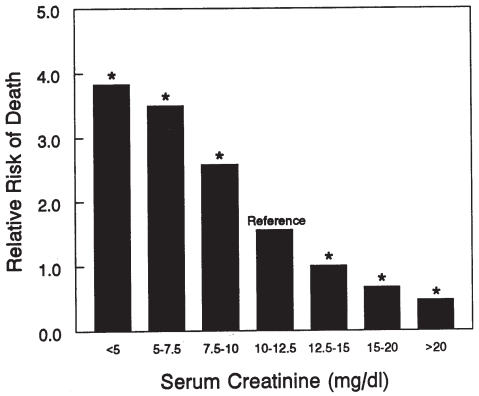

Figure 3. In a large population of HD patients (n = 19,746), serum creatinine concentrations correlated inversely with the risk of death (* $p < 0.0001$). P values refer to each group of patients compared to the reference group with serum creatinine 12.5 – 15.0 mg/dl. Adapted from reference [43] with permission from The American Journal of Kidney Diseases.

Table 2. Indicators of Prognosis

	BUN	Serum creatinine	Kt/V_{urea}
Chronic renal failure	poor	good	poor
Hemodialysis	poor	poor	good
Peritoneal dialysis	poor	poor	good

ance than similar measurements using urea. Like urea, serum creatinine concentrations continue to be measured in hemodialyzed patients, mainly to assess nutrition and muscle mass. In PD patients, solute gradients are insignificant, so the creatinine clearance continues to be used as an index of dialysis adequacy. Similar to HD, serum creatinine levels are difficult to interpret and are mainly reflective of nutrition and muscle mass.

Basis for the Prescription

Transition from Serum Creatinine to Urea Clearance

Table 2 shows the changing reliance on serum levels and clearance of both urea and creatinine as renal function deteriorates. Unlike urea, creatinine production is relatively constant from day to day and is little affected by diet. Also in contrast to urea, creatinine excretion and serum levels are unaffected by urine flow so creatinine clearance is a reasonable indicator of the GFR. For these reasons, serum creatinine levels are watched more closely than urea levels by the physician monitoring renal function in the early stages of kidney failure [55]. As renal function deteriorates further, tubular reabsorption of urea diminishes due to higher filtrate flow rates per remaining nephron, and as a consequence urea clearance more closely approximates the GFR. Despite this improved correlation of urea clearance with GFR, clinicians continue to prefer following the serum creatinine and to a lesser extent the creatinine clearance to determine the need for dialysis as the patient approaches end-stage. Once the patient becomes dependent on the dialyzer, the changing significance of serum creatinine and urea levels, as noted above, forces the physician to follow a different set of rules.

In contrast to native kidneys, artificial kidneys do not secrete or reabsorb solutes in response to volume contraction in the patient, so the serum urea/creatinine ratio loses its significance in this respect. Serum creatinine levels tend to be chronically elevated, out of proportion to urea levels, especially in males, and are disproportionately lower in patients who maintain even small levels of residual renal function. Neither urea nor creatinine

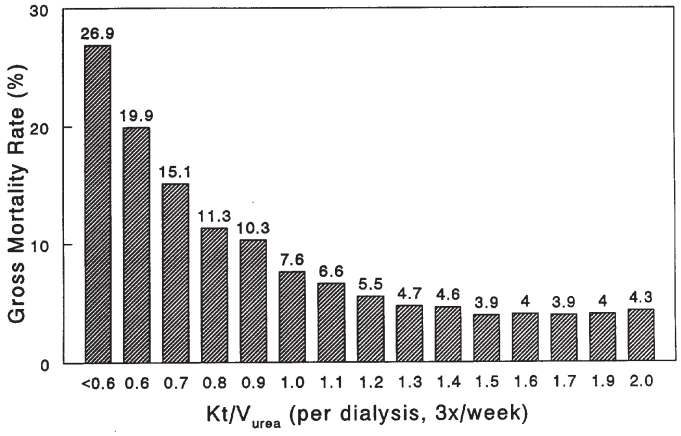

Figure 4. Mortality correlated with Kt/V_{urea} in the 1992 Japanese registry of 42,341 HD patients [62]. Gross mortality is expressed per year for the prevalent patients in each *Kt/V* category. Mortality rates for *Kt/V* values above 1.2 are not significantly different from each other. Graph adapted from reference [62] with permission from The American Journal of Kidney Diseases.

concentration in the serum is a reliable indicator of the need for or success of dialysis. One possible reason for this failure is the confinement within a relatively narrow range of artificial kidney function compared to the relatively wide range of function observed in native kidneys prior to end-stage. Consequently, the generation rate and other factors independent of dialyzer clearance (e.g. protein nutrition and muscle mass) play relatively larger roles in determining solute levels.

Both before and after intervention with dialysis, measurement of *small solute clearance* is an important part of the management of patient with renal failure. Because serum creatinine levels correlate roughly with creatinine clearance in patients with adequate native kidney function, there is less need to measure clearance. In hemodialyzed patients, both serum creatinine and creatinine clearance are difficult to interpret for reasons noted above, so soon after the initiation of HD treatments the nephrologist must transition from reliance on serum creatinine levels to reliance on *urea clearance*. For PD patients both urea and creatinine clearances are used as yardsticks for treatment adequacy, but the serum creatinine concentration cannot be used for this purpose.

Expressing the Dose of Dialysis

As noted above, morbidity and mortality rates are minimized when each patient is given a standard dose of dialysis adjusted for body size. This principle was derived from analysis of the NCDS data and subsequently confirmed by several cross-sectional studies (Figure 4) [42, 30, 52, 62]. In all of these studies, the dose of dialysis was expressed as a clearance, usually given per dialysis rather than per minute (*Kt*), and for each patient the dose was adjusted for body size (larger doses for larger patients). The index of size was not body weight but a close correlate, the volume of urea distribution (*V*), which is equated to total body water volume, usually expressed in kilograms. The adjustment for *V* was a convenient one derived from the mathematics of first order molecular kinetics (see discussion below of the *Dose Denominator*). In nearly all cases the dose is expressed not as a prescribed clearance but as a delivered clearance (*Kt/V*). The distinction between prescribed and delivered doses of dialysis is an important one that is discussed in more detail below. The combined normalization by *V* and measurement of the delivered dose from changes in blood urea nitrogen (BUN) concentrations greatly sim-

Table 3. Possible Determinants of the Need for Dialysis

Factor	Evidence
Patient size	
Weight	Correlates closely with volume
Volume	NCDS [30]
Surface area	A common scaling factor for physiologic functions
Residual native kidney function (K_R)	Mortality rates are markedly affected by K_R [11]
Gender	Males have a higher mortality rate [1]
Pregnancy	Anecdotal [32]
Diabetes mellitus	Mortality data showing that diabetics benefit more from raising the dose [12]
Urea generation rate	Old data showing improvement in uremia with dietary protein restriction without dialysis [28]

plifies the measurement and eliminates several potential sources of error.

Individualizing the Dose

The primary goal of quantifying dialysis is to assure that each patient gets enough. The implication is that patients differ in their needs according to certain identifiable and measurable parameters such as their size and/or gender. Table 3 shows a list of factors that have been considered possible determinants of the need for dialysis in ESRD patients, and are therefore candidates for inclusion in the denominator of any standard adopted for the entire population. Size and residual renal function are the most well accepted of the factors listed in Table 3 and are appropriately included in most models and standards. Although most agree that size is important, the appropriate measure of size is controversial (see discussion below of the *Dose Denominator*). Empirical data suggests that fetal outcome is improved if the dose of dialysis is increased during pregnancy [32]. Limited data have also suggested an increased need for dialysis in patients with diabetic nephropathy [12].

Mortality Rates and Dialysis Adequacy

As more experience is gained with dialysis, it is increasing clear that the amount of dialysis needed for good health is greater than that necessary to maintain life. When the amount of delivered dialysis is sub-optimal, the patient may be asymptomatic early on but the cumulative effects over a longer period of time may cause significant morbidity [30, 39]. In addition, the effects of inadequate dialysis may be difficult to reverse. Patients who were randomized to the lower doses of dialysis of short duration in the NCDS continued to show a proportionately higher mortality rate in the 12 months of follow-up after their therapy was increased, suggesting that recovery from prolonged inadequate dialysis may not always be possible with current dialysis techniques [53].

Advances in the technology of dialysis and in knowledge of the pathophysiology of ESRD over the past 3 decades have improved the quality of life for patients dependent on maintenance dialysis, but mortality and morbidity remain unacceptably high, especially in the United States [33]. For patients in the U.S.

Table 4. Hemodialysis Mortality Rates, 1987*

Country	Mean age (years)	Prevalence (per million)	Annual Mortality (%)
France	54.2	254	7.8
Japan	51.1	671	8.7
EDTA	51.6	280	10.4
West Germany	58.0	320	11.0
Australia	–	152	13.6
New Zealand	–	–	14.2
Sweden	59.0	–	14.7
Canada	54.0	186	16.9
USA	55.5	403	22.8

*adapted from reference [33] with permission from the American Journal of Kidney Diseases

initiating dialysis at age 59 years, life expectancy is approximately equivalent to the same-aged patient with a diagnosis of colon cancer [31]. In 1987, the annual mortality rate was 22.8% for all U.S. dialysis patients compared to rates of 7.8% and 8.7% reported from France and Japan respectively (Table 4). In the U.S., the mortality rate has been slightly but consistently higher in patients managed with PD compared to age-matched patients managed with HD [1]. A recently completed Canadian study of PD that included a large proportion of patients in the U.S. showed significantly worse survival in U.S. patients that was not easily explained, except perhaps by differences in patients' compliance with their dialysis prescriptions [6, 7]. In contrast to the U.S., survival of Canadian HD patients was worse than PD patients.

Self-defeating Aspects of Intermittent Dialysis

Because solute removal is the major goal of dialysis, the non-linear relationship between the intensity of dialysis and solute removal is worth examining in more detail. Doubling the dose does not double solute removal because removal depends on concentration as well as clearance and time, and the concentration falls during intermittent dialysis (Figure 5). Clearance may be high while solute removal is low. As dialyzer blood flow is increased during intermittent HD, diminishing increments in clearance are inevitable. In addition, with each incremental increase in clearance, there is less incremental removal of solute from the patient.

Causes of these additive but self-defeating effects are:

– the fundamental *first order nature of dialysis* itself due to flow and membrane-limited diffusion within the dialyzer and
– *solute disequilibrium* within the patient (see discussion below of *Solute Disequilibrium*). *Access recirculation* is a specialized case of solute disequilibrium that is separately measurable and preventable. *Cardiopulmonary recirculation* (see below) is a predictable form of solute disequilibrium found in all patients with peripheral arteriovenous shunts and absent during vein-to-vein dialysis. Differences

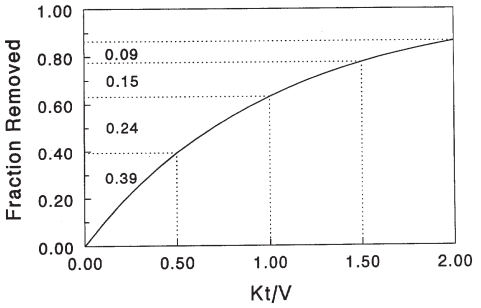

Figure 5. Single compartment analysis predicts diminishing solute removal as *Kt/V* increases from 0 to 2.0. Reprinted from reference [16] with permission from Seminars in Dialysis.

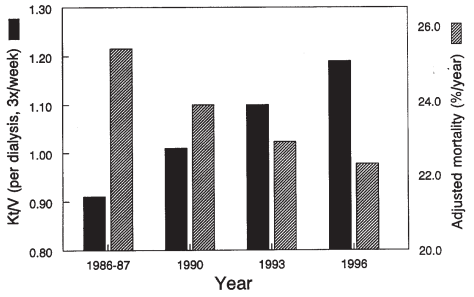

Figure 6. A slight decline in mortality among prevalent HD patients in the U.S. correlated inversely with a significant rise in Kt/V_{urea} from 1986 to 1996. Data from the USRDS [2].

in blood perfusion to tissue volume ratios cause flow-dependent disequilibrium elsewhere in the body and contribute to diminishing efficiency when attempts are made to increase the intensity of HD. Sequestration of urea in quiescent muscle is suspected to contribute to disequilibrium; support for this concept comes from a demonstrated reduction in the magnitude of urea rebound when patients exercise during HD and increase muscle blood flow [56]. Sequestration in skin has been suggested by reduction in urea rebound after warming the patient [14].

Although solute removal is increased by increasing blood or dialysate flow, the increase diminishes with each increment in flow, i.e., the two variables are not linearly related. Manipulation of blood or dialysate flow should be viewed in a proper perspective. Other maneuvers such as increasing dialysis frequency may be more effective as a means of improving dialysis efficiency (see discussion below of *Dialysis Frequency*).

Increasing Doses of Dialysis in the United States

Because the high mortality rates have raised the suspicion that patients in the U.S. have received less than the optimal dose of dialysis, the dose has significantly increased over the past 5 years. Coincident with this increase in dose, a slight decrease in mortality has been observed (Figure 6) [1]. Important remaining questions are, is the improvement in mortality related to the increase in dose and if so, how much more improvement in mortality might be gained if the average dose is increased further? Based on the above discussion about solute kinetics, one would expect that increasing the dose beyond a certain point would not further benefit the patient. At this "optimum dialysis dose", patient outcome would no longer depend on *Kt/V*. The plateau in the outcome curve is expected from a simple consideration of solute kinetics during a single dialysis treatment but it might be enhanced by an adverse effect of dialysis, e.g. by removing a vital solute or exposing the patient to a toxic solute on the dialysate side. A toxic effect of acetate, added to the dialysate as a bicarbonate base precursor, probably simulated this plateau effect in the years before bicarbonate-

based dialysate was available. Acetate is a known potent vasodilator in concentrations readily achieved during HD and was a major contributor to poor tolerance of dialysis in the past. In contrast to increasing the dose per dialysis, increasing the frequency of dialysis has better potential for enhancing the therapeutic effect of dialysis as discussed below.

Yardsticks and Mathematical Models of Dialysis

Clearance

For the nephrologist, clearance is a measure of solute removal from the body either by the native kidney or by the artificial kidney. As an expression of solute removal, clearance is more popular than the raw elimination rate because it tends to measure the process itself, independent of the serum solute concentration. This is important for intermittent dialysis where clearance tends to be constant while solute concentrations (and raw removal rates) fall dramatically and rapidly as a consequence of the dialysis. Expressing solute removal as a clearance is an attempt to normalize the removal rate for first order processes like simple diffusion and filtration, where the rate is directly proportional to (and driven by) the afferent solute concentration (*C*).

$$dA/dt = -KC \quad (1)$$

A is the amount of solute in the compartment = *CV*, i.e., the product of the concentration (*C*) and the volume of the compartment (*V*). *K* is the clearance which is constant for first order processes. If *V* is constant and there is no other addition or removal of solute,

$$dC/dt = -(K/V)C \quad (2)$$

or

$$\frac{dC/dt}{C} = -K/V = -k \quad (3)$$

Equation 3 shows that the fractional removal rate (left side of the equation) at any time during dialysis is constant despite marked changes in *C*. Clearance (*K*) is a constant like *k*, the elimination constant, but unlike *k*, is expressed as a flow. The elimination constant, familiar to pharmacokinetics, expresses solute removal rate as an instantaneous fraction of the amount available or, if *V* is constant, as a constant rate of change in fractional concentration.

Dialyzer Clearance

Dialyzer clearance (K_D) can be defined as the solute removal rate divided by the dialyzer inflow concentration and is a measure of the performance of the dialyzer. K_D is affected in a predictable manner by changes in blood flow (Q_B) and dialysate flow (Q_D), so each of these must be specified when the dialyzer clearance is given. To avoid this inconvenience when comparing dialyzers, nephrologists usually refer to the dialyzer's *mass transfer area coefficient* (K_0A) which is the maximum clearance achievable at infinite blood and dialysate flows rates. K_0A is a function primarily of the membrane since at infinite flow rates the membrane is the only barrier to clearance, which is constant for each dialyzer and solute combination. K_0A can be computed from flow rates and consideration of mass balance across the dialyzer [48].

$$K_0A = \frac{Q_BQ_D}{Q_B - Q_D} ln\left(\frac{1 - K_D/Q_B}{1 - K_D/Q_D}\right) \quad (4)$$

Recently, a positive correlation between K_0A and the dialysate flow rate has been demonstrated for a variety of hollow fiber dialyzers [41]. This additional effect (not included in Equation 4) is probably caused by channeling of dialysate (causing poor equilibration) at low flow rates that disappears at higher rates.

As defined above, dialyzer clearance, also known as *prescribed clearance*, is a real clearance that can be measured precisely from solute concentrations in blood drawn simultaneously from the inflow and outflow of the dialyzer. Because this instantaneous clearance may change during dialysis, to precisely quantify the treatment and assure that the patient received the full benefit of the prescribed dose, multiple simultaneous dialyzer inlet and outlet blood specimens would be required throughout the treatment. Fortunately this is not necessary because the *integrated clearance*, also known as the mean effective or *delivered clearance* achieved during the treatment is easily calculated from the predialysis and postdialysis BUN. However, it is important to note that the delivered clearance is a virtual clearance that is not directly measurable, so the value that is computed depends on the mathematical model of dialysis solute kinetics used to define it. The various models of urea kinetics described below define effective or delivered *dialyzer clearance*, delivered *patient clearance*, and the *continuous equivalent of intermittent clearance* (EKR).

Delivered Dialyzer Clearance: Origin of *Kt/V*

The simplest model of urea kinetics ignores urea generation and volume changes during dialysis, and provides a solution by integrating the mathematical expression of urea mass balance described in Equation 2. Integration of this equation over a period of time (t) gives a familiar expression for concentration (C) of a drug or other solutes eliminated by a first-order clearance mechanism [26]:

$$C = C_0 e^{-Kt/V} \quad (5)$$

$$Kt/V = \ln (C_0/C) \quad (6)$$

K is the integrated clearance per unit of time (t), V is the volume of distribution, and C_0 is the initial concentration. Since K and V are constant, Equation 5 expresses an exponential relationship between concentration and time. Equation 6 is simply a rearrangement of Equation 5 that demonstrates how the integrated clearance can be calculated from two timed concentrations (C_0 and C). When the integrated clearance, averaged between time zero and t, is expressed per "t" unit of time and factored by V, the clearance is expressed as "Kt/V". This expression is apparently dimensionless because the volumes cancel leaving only a fraction per unit of time. It is important to note that the time factor is not eliminated and that this expression is actually a measure of normalized or fractional clearance per dialysis and has units of time^{-1}. Since it represents a measure of the dose of a single dialysis, the schedule of dialyses must be included whenever Kt/V is given as a standard or measure of dialysis adequacy. Note also that the individual components of the expression are not actually measured; only the two serum concentrations are required.

The Meaning of *Kt/V*: Prescribed and Delivered

The now antiquated practice of following the patient's BUN as an indicator of dialysis success has been replaced by a method that focuses on the performance of the dialyzer.

Both the prescribed and the measured or delivered dose of dialysis are expressions of dialyzer clearance. The prescribed clearance is estimated from the following equation, a rearrangement of Equation 4:

$$K_D = Q_B \left[\frac{e^{K_0 A\left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - 1}{e^{K_0 A\left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - \frac{Q_B}{Q_D}} \right] \qquad (7)$$

Clearance is expressed per dialysis (K_Dt) instead of per unit of time, and to allow comparison among patients, K_Dt is adjusted for patient size, expressed as V, the patient's volume of urea distribution, resulting in the expression K_Dt/V or more simply, Kt/V. Normalizing the dose to V is analogous to normalizing a medication dose to patient weight or surface area. V can be approximated from anthropometric formulae or from the mean of several previous kinetic analyses (see *Single Compartment Model* below).

A practical point when adjusting the prescription: since both Q_B and Q_D are located within and outside of the exponential terms in Equation 7, values for Q_B and Q_D must be chosen from a nomogram or derived by iteration of Equation 9 (see below). The latter method requires a computer or programmable calculator. Despite these complexities, Equation 7 is a valuable tool for adjusting the dialysis prescription when a target K_D has been identified from measurement of the delivered Kt/V.

As described above (see *Delivered Dialyzer Clearance*) the delivered dose of dialysis, also expressed as Kt/V, is calculated from BUN measurements prior to and following a given HD treatment. The delivered Kt/V is an integrated clearance that encompasses the entire dialysis and can be considered the fraction of the patient's urea volume that is cleared per dialysis. None of the three terms that make up the expression Kt/V need to be directly measured. Thus Kt/V, although a measure of effective dialyzer performance, is actually a patient-derived parameter.

When applied to urea kinetics, the simplified expression for Kt/V in Equation 6 was derived assuming no changes in the volume of distribution during dialysis and no urea generation. Since neither of these conditions usually apply to therapeutic dialysis, Equation 6 must be expanded to include the additional variables dV and G. Addition of these terms produces a more realistic expression of the single compartment model which is discussed in more detail below.

Single Compartment Model

Because urea is a small highly soluble but uncharged molecule (Figure 1) with low binding affinity for serum and intracellular proteins, it distributes only in aqueous environments and diffuses rapidly among body water compartments. The rate of diffusion is so rapid that, for some approximations, a single space of distribution, i.e. total body water (TBW), can be assumed. Given ample time for distribution, e.g. between hemodialyses when urea accumulates at a slow constant rate, these assumptions are reasonable and single-compartment kinetic models are appropriate. During HD treatments, however, blood urea concentrations change much more rapidly, causing urea gradients to appear (see discussion below of *Multicompartment Models*). If we ignore these gradients, a single pool model for urea mass balance can be described as shown in Figure 7. The rate of change in urea content within the compartment at any moment in time (t) may be computed.

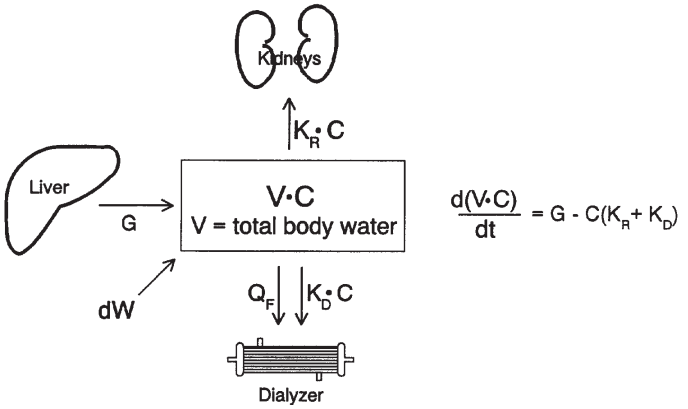

Figure 7. Single-compartment, variable-volume model of urea mass balance. K_R is the residual native kidney clearance, K_D is the dialyzer clearance, G is the urea generation rate, dW is the rate of fluid accumulation between dialyses, Q_F is the rate of fluid removal during dialysis, V and C are the volume and concentration of urea in the single pool. The equation to the right shows the determinants of an instantaneous change in urea mass balance, d(VC)/dt.

$$\frac{d(VC)}{dt} = G - KC \tag{8}$$

where V is the postdialysis urea distribution volume, C is the urea concentration, G is the urea generation rate and K is the sum of dialyzer and native kidney urea clearance (K_D + K_R). Integration of Equation 8 during and between dialyses yields the following equation for urea concentration at any time (t):

$$C = C_0\left[\frac{V - Bt}{V}\right]^{\left(\frac{K_R+K_D+B}{B}\right)} + \frac{G}{K_R + K_D + B}\left[1 - \left[\frac{V - Bt}{V}\right]^{\frac{K_R+K_D+B}{B}}\right] \tag{9}$$

where B is a constant rate of fluid gain (positive between, negative during dialyses). The modeling process begins with measured values of C and C_0 and requires fitting of V and G to Equation 9. G is determined largely from the interdialysis interval when K_D is zero while V is primarily derived from the ratio of the change in C from beginning to end of dialysis and the supplied value for K_D obtained from Equation 7. The resulting value is expressed as "spKt/V", because it is derived from a model of urea kinetics that describes the patient's urea volume as a perfectly equilibrated single pool. Sensitivity analysis shows that spKt/V is very insensitive to the selected values for K_D and the fitted value of G. For example, in a 35 liter patient with Kt/V = 1.3/dialysis and an average fluid accumulation of 1 mL/min between dialyses, as the value for K_D entered into the model varies from 200 to 400 mL/min, spKt/V changes only from 1.33 to 1.26. This simply means that the ratio of K/V is relatively constant (V is proportionate to K) and is determined primarily by the fall in BUN and time on dialysis (Equations 3 and 6).

If V can be determined independently from an anthropometric formula or from the mean of multiple previous urea kinetics modeling, then a comparison with the current modeled V determined from Equation 9 using K_D derived from equation 7 can serve as a measure of dialysis quality assurance. In general the two should agree with an error of no more than 15 – 20%. Most often, if a discrepancy is found, the computed V is larger than the expected V, indicating that the expected dialyzer clearance determined from Equation 7 was not achieved. This is usually caused by errors in blood or dialysate flow or a dialysis timing error. Other causes include loss of membrane surface area or other errors in K_0A.

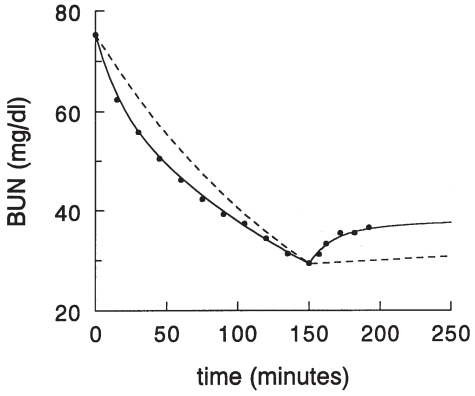

Figure 8. During the course of a HD treatment, the BUN falls in a pattern that is better predicted by a two-compartment model of urea mass balance, as shown by the solid line. The dashed line is the single compartment model prediction. Each data point is a single timed measurement of BUN in a single patient.

Solute Disequilibrium

The Single Compartment Model Fails to Predict the BUN

The assumption that TBW behaves like a single pool is incorrect. Figure 8 shows that the concentration of urea is overestimated during and underestimated immediately following a HD session. The cause of this discrepancy is a resistance to solute diffusion within the patient that causes solute gradients to develop among body water compartments during the relatively rapid removal of urea by the dialyzer. This failure to equilibrate causes the urea concentration in the blood to fall to a lower level than in the remainder of the patient, especially when compared to the intracellular space and in poorly perfused compartments such as the skin and quiescent muscle. Because the concentration of solute in the blood entering the dialyzer is the driving force for dialysis, the efficiency of dialysis falls more rapidly and to a lower level than that predicted by the single-pool model. Mathematically, the dialyzer clearance term (K_D) in the expression for single-pool *Kt/V* overestimates the average "whole body" or patient clearance.

It is important to emphasize that although the *delivered dialyzer clearance* (K_D) is usually accurate when measured using the single compartment model (see discussion below of *Single Compartment Model*), urea disequilibrium reduces the actual delivery of urea to the dialyzer by reducing the blood concentration. The lower urea concentration in blood entering the dialyzer does not lower the dialyzer clearance but reduces the amount of urea removed from the patient below what would be removed in the absence of disequilibrium. As a result, the overall effectiveness of the delivered dialysis falls below that predicted by the single-pool model.

The Single Compartment Model Accurately Predicts K_D/V

Errors in V or K_D are usually not caused by urea disequilibrium, despite the occurrence of easily documented disequilibrium (Figure 8) even during relatively low efficiency dialysis. V is not overestimated because the two major errors caused by solute disequilibrium have opposing effects on V [15]. For a delivered *Kt/V* of approximately 1.3 during a hemodialyses lasting approximately 3 hours, the errors nearly completely balance one another, giving an accurate measure of V [13, 29]. For more prolonged dialysis or less intense dialysis (lower *Kt/V*), V is slightly underestimated and for shorter or more intense dialysis, V is slightly overestimated by the single compartment model. Because of these offsetting errors, the single compartment model of HD urea kinetics serves well to measure the effective (delivered) dialyzer clearance.

The NCDS and subsequent studies showed that guaranteeing a minimum effective *dialyzer clearance* (K_D) per treatment on a regular basis in each patient minimizes individual risk from the consequences of ESRD. Because the single compartment model is simple to use and gives a reasonably accurate measure of *dialyzer clearance* per treatment factored by V (spKt/V), it has become the standard for prescribing HD and evaluating its adequacy. If the goal of kinetic modeling is to define more precisely the effect of dialysis in the patient, then additional steps must be taken to measure *patient clearance*.

Patient Clearance

Patient clearance is more difficult to define. The concept is simple and intuitive but the mathematical definition appears at first to be complex. Movement of solute from the patient to the dialysate occurs by a first-order process (diffusion), but the rates vary among tissue compartments. Patient clearance can be considered the removal rate divided by the average of all solute concentrations within the patient's tissue compartments. It is always lower than dialyzer clearance because tissue concentrations are always higher than the concentration in blood entering the dialyzer. Dialyzer clearance is a good measure of dialyzer performance, but patient clearance is a valuable measure of the overall effectiveness of the dialysis where it counts, in the patient. For example, if blood concentrations fall sharply below tissue concentrations during HD, the dialyzer clearance may be exemplary while patient clearance and removal of solute from the patient is relatively impaired.

Mean patient clearance can be measured by integrating the instantaneous patient clearances over the course of a dialysis. This would require knowledge of all tissue compartment concentrations and volumes at multiple times during the dialysis treatment. Fortunately there is a simpler technique for measuring mean patient clearance. If we ignore the multiple concentration gradients within the patient during dialysis and simply consider to patient as a black box, mean patient clearance (K_P) can be calculated from the predialysis concentration (C_0) and the final equilibrated postdialysis concentration (C_E). Assuming that following equilibration, the patient is a well-mixed solution of constant volume V, and that C_E is measured after complete equilibration among compartments, and that G is negligible, patient clearance (K_P) is (analogous to equation 6):

$$K_P = \ln(C_0/C_E)V/t \qquad (10)$$

Equilibrated *Kt/V* (e*Kt/V*)

The weakness of spKt/V as an expression of the effectiveness of HD has led to a more realistic measure of whole body or equilibrated Kt/V derived from the patient clearance also called eKt/V *or patient* Kt/V:

$$eKt/V = \ln(C_0/C_E) \qquad (11)$$

Like spKt/V, eKt/V is also a measure of fractional clearance of urea per dialysis but the patient clearance is substituted for the dialyzer clearance (K). The "e" in eKt/V denotes an equilibrated Kt/V since, as noted above, patient clearance represents the effective clearance of urea after equilibration is taken into account. eKt/V is calculated in the same way as spKt/V except that C_E is substituted for the immediate postdialysis BUN. It is worth noting that eKt/V is a virtual clearance for which there is no concrete measurable counterpart. In contrast, spKt/V is a measure of the integrated dialyzer clearance,

a clearance that may be measured directly across the dialyzer at any time during the treatment. Barring difficulty with the dialyzer or flow rates across the dialyzer, spKtV is equivalent to dialyzer clearance which should remain constant throughout the treatment.

Measuring *eKt/V*

Unfortunately, the additional time required of the patient and of the staff to obtain the one half to one-hour post-dialysis blood sample to measure C_E is prohibitive and renders this method impractical at best. The inconvenience and cost to obtain the equilibrated sample are difficult to justify. Consequently, alternative methods for measuring e*Kt/V* have been introduced that do not require waiting for solute equilibration to occur. These include collecting and measuring urea removed in a total collection of dialysate, in multiple samples of dialysate, or as a continuously recorded concentration profile; measuring multiple samples of blood during dialysis; and applying mathematical formulae to approximate e*Kt/V* from sp*Kt/V* based on parameters known to influence the magnitude of rebound. A recent comparison of these methods in a large sample of well controlled dialyses showed that a simple linear formula for e*Kt/V* based on sp*Kt/V* and the fractional rate of urea removal during dialysis (*rate method*) gave values for e*Kt/V* closest to that calculated from the equilibrated BUN obtained 30 minutes to an hour postdialysis:

$$e\mathit{Kt/V} = sp\mathit{Kt/V} - 0.60(K/V) + 0.03, \quad (K/V \text{ expressed in hours}^{-1}) \qquad (12)$$

For patients without peripheral A-V access, the relationship to *K/V* was less steep:

$$e\mathit{Kt/V} = sp\mathit{Kt/V} - 0.42(\mathit{K/V}) + 0.02, \quad (\mathit{K/V} \text{ expressed in hours}^{-1}) \qquad (13)$$

Equations 12 and 13 show that if sp*Kt/V* remains constant, e*Kt/V* will decrease as the intensity of dialysis (*K/V*) is increased or as dialysis time is shortened. These equations also suggest that urea rebound and therefore urea disequilibrium are predictable and that rebound is determined primarily by the intensity of dialysis, defined as *K/V*. A practical advantage of Equations 12 and 13 is that no additional samples of blood or dialysate are necessary since *K/V* can be determined from sp*Kt/V* and *t*. This eliminates the inconvenience to patients and the cost to dialysis facilities otherwise incurred in attempts to accurately measure either the equilibrated postdialysis BUN or dialyzer clearance. Note that to determine e*Kt/V*, sp*Kt/V* must be measured. This allows a comparison of the current single-pool standard (sp*Kt/V*) with the more accurate dose based on the patient clearance and equilibrated urea concentrations (e*Kt/V*).

Value of e*Kt/V*

Current standards are based on sp*Kt/V*, not e*Kt/V*. Only recently has the practicality of e*Kt/V* measurements been shown, and no studies have compared the relative outcome predicting powers of the two expressions of dialysis dose. Arguments against using e*Kt/V* as a measure of dialysis and of dialysis adequacy are listed in Table 5. Fundamentally, use of e*Kt/V* takes time (duration of dialysis) into consideration, granting a bit more dialysis (higher e*Kt/V*) to the patient who remains on the treatment longer with a lower clearance but with the same sp*Kt/V*. We hope that future studies will clarify the value of this additional refinement in the expression of dialysis dosage.

Table 5. Using e*Kt/V* to Measure Dialysis

Arguments against
- No standards have been established.
- The equilibrated BUN is difficult and impractical to measure.
- Dialyzer clearance has already been shown to correlate with morbidity and mortality; why complicate the measurement?
- Adjustments in the dose require a measure of dialyzer clearance, not patient clearance.
- Disequilibrium in the patient is different for every solute. Measuring eKt/V for urea does not guarantee equal compensation for the disequilibrium of other solutes that may be more toxic than urea.

Arguments in favor
- e*Kt/V* is a true measure of the effect dialysis has in the patient.
- Expressing the dose as e*Kt/V* compensates for differences in the length of each dialysis that are independent of sp*Kt/V*.
- e*Kt/V* is easily estimated from measurements of sp*Kt/V* and dialysis time.
- Conversely, sp*Kt/V* can be calculated from e*Kt/V* to allow adjustments in the dose.
- Although it does not account for the greater disequilibrium expected in other solutes, e*Kt/V* comes closer to it than sp*Kt/V*.

The Urea Reduction Ratio (URR)

The urea reduction ratio or URR has been used as a simplified measure of the dialysis dose [35, 44, 45]. URR is defined as the fall in BUN divided by the predialysis BUN and includes the most significant factor that determines *Kt/V*, the ratio of postdialysis to predialysis BUN. Although highly correlated with *Kt/V* in population studies, URR fails to reflect the actual dose received by an individual patient as shown in Figure 9. Convective losses of solute during dialysis contribute to the overall effect of the treatment but are not reflected in URR because they are not accompanied by a change in urea concentration. In fact, whenever losses occur without a change in concentration, URR is zero, as it is for continuous PD and for native kidney function. For patients undergoing intermittent HD, it is possible to receive adequate treatment when the URR is below the standard or conversely, to receive inadequate treatment when URR is above the standard. For a patient with a *Kt/V* of 1.3 and no fluid loss during dialysis, URR is 0.71; whereas if fluid loss is 10% of body weight, URR is 0.63 (Figure 9). In contrast to *Kt/V*, URR does not provide a measure of protein catabolism or residual clearance and offers no logical method for correcting a prescription that is inadequate. For these reasons, URR was not considered acceptable by the National Kidney Foundation/Dialysis Outcomes Quality Initiative (NKF/DOQI) Hemodialysis Adequacy Work Group as a measure of, or as a standard for, dialysis. On the other hand, in the absence of other measures of dialysis, URR is much better than simply following the BUN. It is also important to note that the major work associated with determining either *Kt/V* or URR is spent in collecting and analyzing the predialysis and postdialysis blood samples. Therefore URR is less of a practical simplification than a mathematical simplification.

The Solute Removal Index (SRI)

The yardsticks of dialysis discussed above are all based on the effects of dialysis on the blood concentration which can be fairly com-

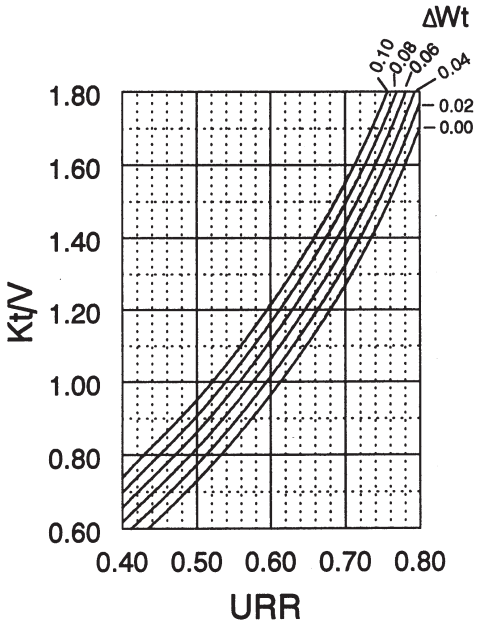

Figure 9. When *Kt/V* is constant, the urea reduction ratio varies with fluid removal during dialysis. For example, if *Kt/V* is 1.2 per dialysis, URR varies from 0.60 to 0.68 as fluid removal varies from 0 to 10% of body weight.

plex. A more direct approach that has potential for simplifying the measurement of dialysis is the method of dialysate analysis, i.e. measuring the total amount of solute removed during the treatment. If removal of urea or another solute is measured, the result can be expressed either as a clearance, i.e. the amount removed divided by the mean concentration; or, similar to the expression for URR, as the amount removed divided by the initial amount present in the patient at the beginning of the treatment. This approach is analogous to the measurement of clearance and first-order processes in general because the amount removed depends on the starting amount, other things being equal. So using the starting amount as a denominator to normalize the dose is reasonable, although not as mathematically logical as the log mean concentration used as the denominator for clearance. The dialysate method is discussed in more detail below. SRI has advantages over URR as a measure of dialysis because it includes removal of solute by ultrafiltration and residual clearance. For continuous dialysis, SRI is equal to *Kt/V*, whereas URR is zero.

Multi-compartment Models

As noted above, the patient presents a resistance to dialysis, the magnitude of which has only recently been appreciated. To more realistically model the movement of solute within the patient during dialysis and to better approximate the measured BUN levels during and immediately following dialysis, the mathematical model must be more complex than the simple single pool model shown in Figure 7. Models based on the resistance to diffusion between the blood and tissue compartments and on differences in the relative blood flow to water volume ratio among body compartments have been developed [15, 54, 57, 58].

The Classic Two-compartment Model

In Figure 10, the patient is considered to be divided into 2 pools of water, with a finite conductivity between the pools shown as K_C, the intercompartment mass transfer area coefficient. K_C has units of mL/min, similar to clearance and could be considered the patient equivalent of K_0A. This classic two-compartment model is designed with the intracellular and extracellular water pools as prototypes for the 2 compartments and the cell wall as the major, although not the only, resistance to diffusion of urea. The differential equations describing the classic two-compartment pool model are only slightly more complex than Equation 8.

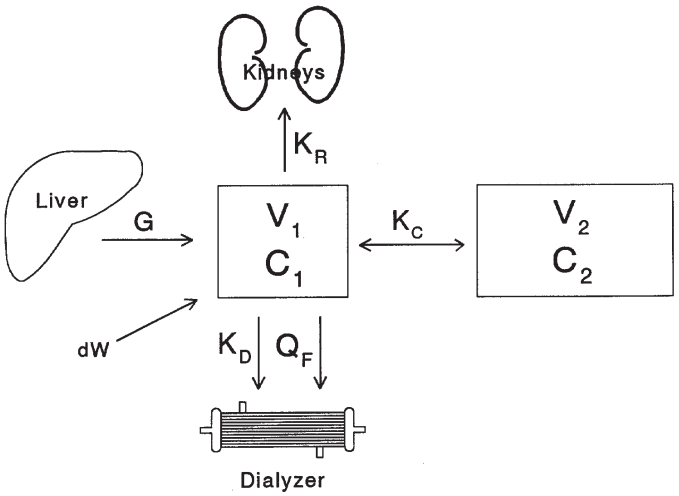

Figure 10. Two-compartment, variable-volume model of urea mass balance. In addition to the symbols shown in Figure 7, V_2 is the volume of the second (remote) compartment and K_C is the intercompartment mass transfer area coefficient. Reprinted from reference [15] with permission from Kluwer Academic Publishers.

The Convection Model and Cardiopulmonary Recirculation

More recently, a different approach, based on differential blood flow rates among body tissues, has been taken to modeling urea disequilibrium during HD (Figure 11). This model includes the component of disequilibrium due to cardiopulmonary recirculation that the classic model fails to predict, and it accounts much more precisely for the early rapid fall in BUN during HD. The overall effect on patient clearance, however, is similar and not distinguishable from the older classic model. Although the relative contributions of flow and diffusive resistance have not been quantified, it is clear that the 2 are additive. This leads one to conclude that tissue resistance to urea diffusion is lower than had been assumed in the past based on predictions of the classic model. Neither of these more complex models is currently used in clinical practice, but it is possible to simulate their effects on *Kt/V* using the rate equation (see measurement of e*Kt/V* above).

Dialysate Methods

Hemodialysis

One of the advantages of intermittent HD is the easy method it provides for measuring dialyzer urea clearance, urea generation, and the patient's volume of urea distribution with simple blood measurements without the need for collecting dialysate, i.e. without measuring what is removed. This convenience is not available to patients with continuous kidney function, either native or replacement, where collections of urine and dialysate for measurement of clearance are usually required. However, measuring changes in blood concentration requires careful timing of the postdialysis blood sample to avoid errors from postdialysis rebound and from recirculation of blood through the access device. It also requires complex mathematical interpretation and multiple blood samples if one intends to precisely account for solute disequilibrium in the

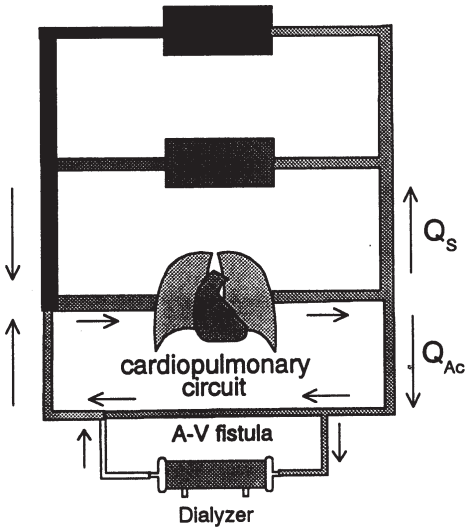

Figure 11. In contrast to the classic diffusional model of urea kinetics shown in Figure 10, this model is based only on blood flow in the patient. Gradients for urea appear in the blood compartment during HD because of differing rates of perfusion among body tissues. Even in the absence of any diffusion barriers, this model predicts a rapid fall in BUN at the beginning of dialysis and a sharp rebound following the end of the treatment. The rapidly circulating blood compartment is the cardiopulmonary circuit through the peripheral A/V access device.

patient. Measuring the dose of dialysis on the dialysate side is more direct and constrained by fewer assumptions, so there are fewer pitfalls and the results are theoretically more reliable and reproducible. Virtually all of the parameters that are measurable on the blood side are also available from dialysate methods, including K_D, V, PCRn, $K_{C,}$ and eKt/V. In contrast to blood-side methods that estimate dialysate removal, dialysate methods directly measure removal, which may then be used to estimate blood concentrations including the equilibrated postdialysis BUN. The latter estimate eliminates the necessity for drawing this problematic blood sample (see discussion below of rebound).

Because collection of the total dialysate is impractical, automated methods have been developed for measuring dialysate urea concentrations either continuously or at frequent intervals during treatment [3, 18, 24, 37]. Automated techniques for real-time monitoring of dialysate offer the clinician (and the patient) an immediate feedback, even before the dialysis is completed. On-line methods can also provide a precise delivered dose of dialysis during each treatment by adjusting the dialysis prescription concurrently. Dialysate flow is also more easily and directly measured by collecting timed samples.

To quantitate dialysis using dialysate measurements, the most logical index of adequacy is the solute removal index (SRI) defined above. To calculate SRI for urea, the dialysate urea, the predialysis BUN, and the patient's urea volume (V) must be measured. Predialysis levels can be determined by equilibrating the dialysate with the blood before starting the procedure and the patient's urea volume, which is relatively constant, can be measured infrequently from dialysate measurements:

$$V = \frac{Q_D C_D t - DVC_0 - t(G - K_R C_{AV})}{C_0 - C_E} \qquad (14)$$

where Q_D is total dialysate flow including the ultrafiltration component; C_D is the dialysate urea nitrogen concentration; C_0 is the predialysis BUN; C_E is the equilibrated postdialysis BUN; ΔV is the fluid lost during dialysis; K_R is the native kidney clearance; and C_{Av} is the log mean urea concentration during dialysis. An adjustment in the serum urea concentration is required to convert to serum water concentration. K_D may be estimated as the removal rate ($Q_D C_D$) divided by C_{Av} or from fitting a curve to multiple dialysate concentrations (Figure 12) [37]. eKt/V may then be calculated from each of its components or from a simplified equation:

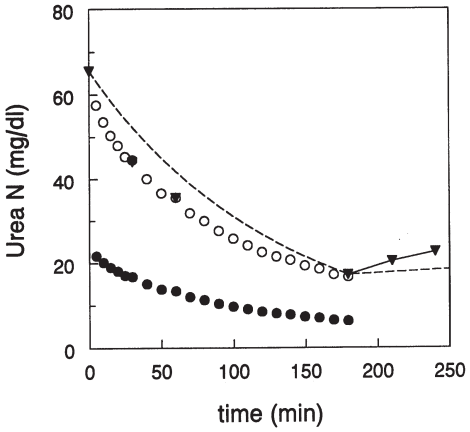

Figure 12. Urea concentration profiles in the blood and dialysate during HD. Solid circles are the measured dialysate concentrations, open circles are the calculated blood concentrations, closed triangles are measured blood concentrations and the dashed line is a prediction of blood concentrations by the single pool model. The dialysate profile may also be modeled to calculate a clearance and assess adequacy of the dialysis.

$$e\mathit{Kt/V} = -\ln(1 - \mathrm{SRI}) \qquad (15)$$

Compared to the analogous equation that uses URR instead of SRI, Equation 15 is more accurate but it also underestimates *Kt/V* when ultrafiltration occurs during dialysis. Once *V* is determined, C_E may be estimated as:

$$C_E = \frac{C_0(V + DV) - t(Q_D C_D - G + K_R C_{AV}}{V} \qquad (16)$$

Error Magnification

Compared to blood-side methods, dialysate methods suffer from an inherently larger error when used to measure the dose of dialysis because to determine e*Kt/V* they require subtraction of two relatively large quantities, the amount of urea in the patient predialysis and the amount removed. The resulting percentage error is considerably larger than usual measurement errors and gets larger as the dose of dialysis increases (high e*Kt/V*). Although the dialysate method is attractive for other reasons, both theoretical and observational data show that it can cause much larger errors in both SRI and e*Kt/V* than blood-side methods [17]. The error in e*Kt/V* is smaller when estimated on the blood side because BUN levels are directly measured both before and after dialysis. The magnified subtraction error inherent in the dialysate method can be minimized by automated techniques that measure the dialysate concentrations multiple times throughout the treatment, fitting a curve to urea concentration profile. The fitted curve allows a more accurate estimate of the amount removed as well as the equilibrated postdialysis concentration.

Peritoneal Dialysis (PD)

As noted above, quantitation of continuous dialysis modalities such as native kidney function and continuous PD requires collection of dialysate and urine. The advantageous fluctuations in urea concentration that allow simplified quantitation of HD do not occur during continuous PD, but their absence offers a clinical advantage for the patient by eliminating solute disequilibrium. The elimination of fluctuations in the BUN improves the efficiency of dialysis and also allows more simplified and unified expressions of the dialysis dose that were discussed above. For example, in patients dialyzed continuously, sp*Kt/V*, e*Kt/V*, and SRI are all equivalent and the magnified subtraction error mentioned above for SRI measured during HD is all but eliminated because of the relatively prolonged period of dialysate collection (usually ≥ 24 hours). There is no postdialysis rebound, no

cardiopulmonary recirculation, and patient clearance can be considered equivalent to dialysis clearance. Because disequilibrium is absent, creatinine clearance can be measured as easily as urea clearance and the patient's residual native kidney clearance, measured either as creatinine or urea clearance, may simply be added to the dialysis clearance to obtain the total clearance. The burden of measurement is shifted from the lab to the patient who must supervise the relatively prolonged collection of dialysate and urine, so measurements of PD are usually not performed as often as measurements of HD. Because they are collected over ≥ 24 hours, peritoneal measurements are theoretically more stable and reproducible than typical HD clearances, although this question has not been directly addressed.

Traditionally, PD has been quantified using urea *Kt/V* per week or using the weekly creatinine clearance. Either may be expressed as *Kt/V* or as an unmodified clearance but neither can be compared directly to HD clearance. Intermittent clearance cannot be compared directly to continuous clearance because of its intrinsic inefficiency that requires a larger dose to achieve the same effect. Intermittent clearance is compared with continuous clearance in more detail below (see *Dialysis Schedule*).

Importance of the Protein Catabolic Rate

In the era preceding the availability of therapeutic dialysis, restriction of dietary protein intake was the only treatment for patients with advanced renal failure [27, 28]. Maintaining caloric intake while restricting protein by prescribing diets high in carbohydrate and fat content was felt to prolong life by reducing the burden of uremic toxins, most of which were thought to originate from dietary protein. When dialysis became available, as a logical extension of the previous therapeutic policy, it was assumed that restricting protein intake should reduce the requirement for dialysis. So the apparent adverse effect of a low protein catabolic rate demonstrated by the NCDS was surprising. Although dietary protein intake was not controlled in a randomized prospective way in this study, the data suggested that it wasn't enough to control the BUN; outcome depended on how the BUN was controlled. Lowering the BUN by dialysis improved outcome whereas lowering the BUN by diet appeared to worsen outcome (Figure 1). PCRn was second only to the BUN itself as a predictor of morbidity. It was this finding that led to the current policy of ignoring the absolute level of urea and instead providing a minimum dose of dialysis, measured as a normalized urea clearance per dialysis given 3 times weekly, as the standard to assure adequacy of the treatment.

This new policy shifted the serum urea nitrogen concentrations from a potential indicator of need for dialysis to a marker for dialyzer clearance. The reliance of this quantification method on urea clearance popularized the technique of urea kinetics modeling which simplifies the measurement of effective clearance integrated over the entire dialysis. In addition to *Kt/V*, the kinetic modeling process also provided a measure of PCRn, a parameter that is important to follow because is too correlated with morbidity. Whether modifying the protein catabolic rate by dietary or other intervention will improve outcome has not been shown conclusively, but if malnutrition is the cause of a low PCRn one would expect that correcting the cause of the malnutrition would improve outcome. Often it is not

enough to simply supplement the diet with calories and protein; correcting underlying heart failure or an inflammatory state may be the more effective treatment.

Measurement of PCRn

Urea is an end-product of protein nitrogen metabolism, so its appearance can be directly translated to net protein catabolism [8]:

$$PCRn = 5420G/V + 0.17 \quad (17)$$

As shown in Figure 13, PCRn is determined mostly from the change in BUN between dialyses measured by the gradual rise in BUN during this period. On the practical side, as shown below, measurement of the third BUN is not necessary.

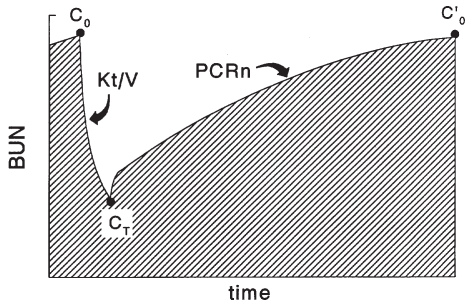

Figure 13. BUN profile during and between dialyses. *Kt/V* is determined largely from the change in BUN during dialysis while PCRn is a function of the change in BUN between dialyses but can also be derived from *Kt/V* and the absolute level of the BUN as shown in Figure 14. The shaded area represents the patient's urea exposure or time-averaged BUN.

The Two-BUN Method of Modeling

Figure 14 shows an extension of urea modeling that allows measurement of both *V* and *G* with only 2 BUN measurements. Since *V* and *G*, the 2 unknown variables in Equation 9, cannot be explicitly resolved (no single solvable equations), an iterative process is required. The two-BUN method shown in Figure 14 simply extends the iteration to cover an entire week instead of a single inter-dialysis interval. This method uses the predialysis BUN twice, first to measure *Kt/V* from the ratio of predialysis to postdialysis BUN and second to measure G and PCRn from its absolute value. The process shown in Figure 14 requires a computer, the slowest of which usually completes the resolution of *G* in under one second.

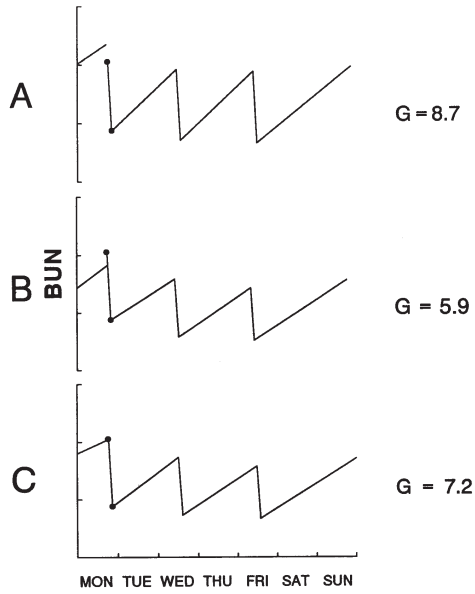

Figure 14. Two-BUN method for calculating *G*. The computer repeats the calculation of *C* for an entire week using Equation 9 and adjusts *G* until the predialysis BUN after one week of calculations matches the measured value. Reprinted from reference [15] with permission from Kluwer Academic Publishers.

Importance of the Dialysis Schedule

There is a growing interest in scheduling HD more frequently than the current almost universally applied 3 per week pattern. When intermittent dialysis is applied more often, the effects of disequilibrium are less prominent and the dialyzer is more efficient at removing solute from the patient. If the goal of dialysis is to maintain solute concentrations below a threshold level, then more frequent dialysis is better because, as shown in Figure 15, it allows a lower average clearance per week. Figure 15 also shows the effect of solute disequilibrium. As K_C, the intercompartment diffusion coefficient decreases, signifying increased resistance to diffusion, the effect of higher frequency dialysis is more prominent. Even for urea, which diffuses among body compartments with seemingly little resistance, the required *Kt/V* per week is significantly lower when dialysis is applied daily compared to 3 per week. Advances in dialysis technology have improved the dialyzer but not the resistance to diffusion in patient.

Theoretically a solute with no resistance to diffusion in the patient (infinite K_C in Figure 15) will show this effect because the dialyzer itself is more efficient when solute levels are relatively constant. Paradoxically, the inefficiency of the dialyzer is enhanced as dialyzer permeability and clearance increases. Increasing the frequency has potential for improving the efficiency of dialysis by diminishing the effects of both patient-dependent disequilibrium and the intrinsic first-order inefficiency of the dialyzer.

To allow comparison of dialysis doses among patients treated with different frequencies, a parameter known as the continuous equivalent of renal clearance (EKR) has been suggested and is discussed in more detail below under *Standards for Dialysis*.

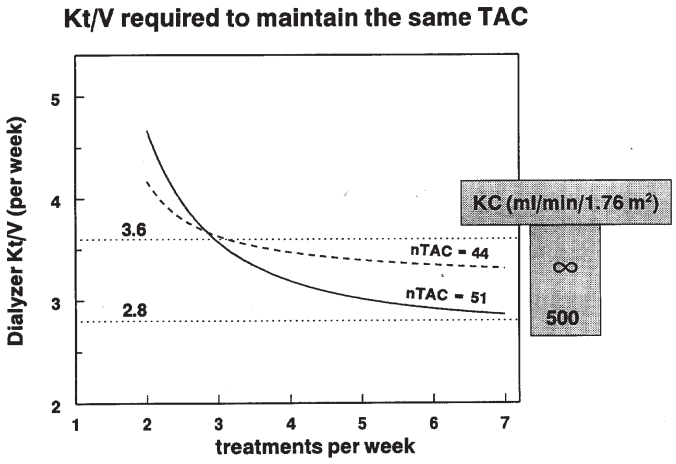

Figure 15. To maintain the time averaged BUN constant, the dose of dialysis provided per week may be reduced as the frequency of dialysis increases. The solid line shows the required weekly *Kt/V* for urea based on a K_C of 500 mL/min. Even a simple single compartment model with no resistance to diffusion in the patient (infinite K_C-dashed line) shows a dependence of weekly *Kt/V* on dialysis frequency.

Standards for Dialysis

NCDS, NIH Consensus, RPA, and NKF-DOQI Guidelines

Although the NCDS was not designed to develop standards for HD, the results permitted such an analysis. Using a mechanistic approach to the data, Gotch and Sargent concluded in 1985 that providing a minimal Kt/V_{urea} for patients thrice weekly would assure adequacy [30]. Since then the equipment and mode of delivery of HD has improved considerably allowing less strict acceptance criteria, and as a consequence the average age has increased and the patients are sicker from other comorbid diseases. Consequently, this preliminary minimum standard was revised upward to 1.2/dialysis in 1993 following a consensus development effort sponsored by the National Institutes of Health (NIH) [51]. Although no controlled data were available to support this dose, the minimum standard for HD was subsequently endorsed by the Renal Physicians Association (RPA), the National Kidney Foundation (NKF), the American Association of Kidney Patients, and several equipment vendors [6, 51, 63]. In addition, the NKF prepared guidelines for the care of dialysis patients as part of the Dialysis Outcomes Quality Initiative (DOQI) that included instructions on such issues as how to calculate the dose of dialysis, how to draw the postdialysis BUN, and how to monitor the blood access device. These guidelines also included a preliminary recommended minimum standard for PD based on several recent studies that showed a continued improvement in morbidity and mortality as the dose of dialysis increased to the 2.0 – 2.2 per week range. These guidelines were published in late 1997 [20, 21].

Standards for Different Schedules: a Universal Approach

Figure 15 shows that it is not possible to compare values for *Kt/V* among patients dialyzed at different frequencies. This variation in dialysis efficiency at different frequencies probably explains the difference in standards for intermittent HD compared to continuous PD: higher frequency dialysis (continuous can be considered an infinite frequency) is more efficient. To permit comparisons among patients dialyzed with different schedules, an index of dialysis has been developed that is independent of schedule. This parameter, the continuous equivalent of renal clearance (EKR), is conceptually simple [10]; it represents the continuous clearance required to achieve the same average solute level in the patient. EKR is also mathematically simple; it is the average solute removal rate divided by the average solute concentration, which is the classical definition of clearance. In stable patients whose urea losses are matched by their protein intake, the urea generation rate (G) can be substituted for the removal rate and the average urea concentration in intermittently dialyzed patients is the time-integrated or time-averaged concentration (TAC).

$$EKR_{urea} = G/TAC \quad (18)$$

PCRn can be substituted for G using Equation 17 and time can be stretched to a week to give the weekly equivalent of Kt/V_{urea}:

$$EKRn = 10.08(PCRn - 0.17)/(5.42\ TAC) \quad (19)$$

where EKRn is the normalized EKR expressed as a fraction of V per week. Both G (or PCRn) and TAC are calculated from formal urea kinetics modeling but are not easily obtained by other means. EKR can be expressed either in terms of Kt/V (a fractional or normalized clearance) as in equation 19 or as a conventional clearance expressed as vol-

umes per unit of time (e.g. mL/min) as in Equation 18. As calculated using either Equation 18 or Equation 19, EKR is a total clearance that, like continuous clearance, can be broken into its constituents, residual native kidney clearance (K_R) and dialyzer clearance (K_D), by simple subtraction. For example, if EKR_{urea} is 12 mL/min and KR is 3 mL/min, the dialyzer contributes 9 mL/min. Expressed as a normalized clearance, if EKRn is 2.0 per week, and residual clearance is 0.6 per week, then the dialyzer contribution is 1.4 per week. These simple additions and subtractions are not possible with either sp*Kt/V* or e*Kt/V* for intermittent dialysis.

The single compartment model overestimates *G* and underestimates TAC, causing an overestimation of EKR as calculated using Equation 18. Therefore, to calculate EKR accurately from values for *G* and TAC provided by formal urea modeling, consideration must be given to disequilibrium using a two-compartment approach. The *rate equation* (Equation 12 or 13) can be used to make the downward adjustment in *Kt/V* from which Ceq, TAC, and *G* can be recalculated. Using the rate equation for this purpose is justified if the duration of dialysis and clearance are comparable to thrice weekly schedules (e.g. 2 – 4 hours, 200 – 300 mL/min in an average-sized adult).

For intermittent dialysis, EKR is always lower than the patient clearance (e*Kt/V*), the difference representing the efficiency of continuous compared to intermittent scheduling. However, if one compares the current minimum standard clearance for PD (Kt/V_{urea} = 2.0 – 2.2/week) to the consensus-derived minimum standard clearance for HD (Kt/V_{urea} = 1.2/dialysis, thrice weekly), adjustments for urea disequilibrium and inefficiency of intermittent dialysis do not completely explain the discrepancy. EKRn, even when the proper adjustments are made for disequilibrium, is approximately 2.8 per week in a patient whose HD provides a urea *Kt/V* of 1.2/dialysis, thrice weekly. Although 2.8 is closer than 3.6 (3 × 1.2) to the 2.0 – 2.2 range targeted for PD, it remains significantly higher. A possible explanation for this discrepancy is that urea exhibits less disequilibrium than the average real uremic toxin.

Although EKR is attractive as a universal expression of dialysis dose, at the current time there are no standards for EKR and regulatory agencies in the U.S. currently demand either *Kt/V* or URR to document dialysis adequacy. Another potential problem with EKR is the lack of an easy method for correcting a dialysis dose that does not meet the target. Conversion to sp*Kt/V* is required to allow changes in the dialyzer clearance or time.

Since EKR is a continuous function, it can be compared directly to native kidney function in a patient prior to initiating renal replacement treatments for ESRD. The benefit of supplemental dialysis can be compared to the patient's dwindling native kidney function and a more rational plan developed for timing the intervention. Population studies of EKR may shed more light on the optimal time to initiate dialysis.

The Denominator for Expressing the Dose of Dialysis

Table 3 shows several currently recognized and suspected factors that modulate the need for dialysis. Expressing the dose as *Kt/V* and establishing a standard based on this value essentially ignores the other potential factors listed in this table and others that may not be listed. *Kt/V* can be adjusted for K_R using several suggested methods, including the EKR method mentioned above, but among the other factors listed, only size is included in *Kt/V*. Patient size is a logical denominator, as

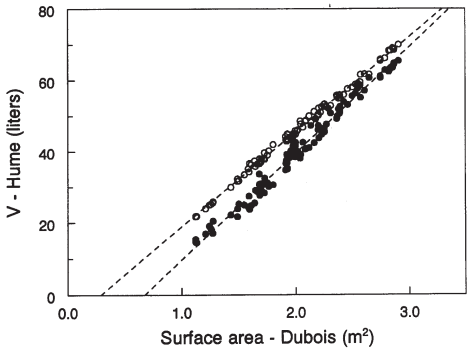

Figure 16. The Hume formula for total body water correlates closely with surface area but differs for men and women. For a given surface area, men (open circles) have more water volume than women (closed circles) [22, 34]. Random data generated using heights 120 – 220 cm, weights 30 – 150 kg.

larger patients are expected to require a higher clearance, analogous to native kidneys, but the appropriate index of size remains controversial. The use of *V* as a denominator is simply a mathematical convenience that, because it correlates strongly with many other size dimensions such as height, weight, and surface area, is probably close to if not an exact match to the most appropriate size denominator. In a patient with constant *G*, however, *V* has little effect on the steady-state solute concentration as shown in Equation 18. A logically more appropriate denominator of size is *G*, the toxin generation rate, not to be confused with urea generation (G_{urea}). Current evidence suggests that *G* is more closely correlated with surface area than with *V*. If this reasoning holds true then we may have to make adjustments to *Kt/V* based on surface area to volume ratios as shown in Figure 16.

Adjusting *Kt/V* for K_R is logical but is rarely done. Most nephrologists prefer to begin dialysis with a dose that is more than adequate to avoid future stepwise increments, usually translated to the patient as an increase in time on dialysis, and interpreted negatively by the patient. If K_R is not measured and ignored in the prescription of *Kt/V*, the patient will be protected from underdialysis but outcome comparisons among patients will not be possible.

Practical Application and Pitfalls of Urea Modeling

The last 2 decades of experience with urea modeling have uncovered a number of pitfalls, most of which can be easily avoided. Usually these problems surface when the results of a patient's urea kinetics analysis do not meet expectations or deviate from previous results (see *Troubleshooting* below). One of the most common sources of error in hemodialyzed patients is in the method for obtaining the post-dialysis blood sample.

When to Draw the Post-dialysis BUN and Why

When drawing the post-dialysis blood sample, care must be taken to avoid artifacts from dilution of the sample with intravenous fluids (saline, blood, and other solutions), often given near the end of the treatment, or from local access recirculation. Care must also be taken to avoid rebound which may begin less than 10 seconds after stopping the blood pump. The instability of the post-dialysis BUN due to these influences necessitates precise timing of the sampling within a short window measured in seconds to minimize errors in the modeled parameters including *Kt/V*. Unless an equilibrated sample is sought, the blood should be drawn at the precise end of the dialysis but precautions must be taken to eliminate the potential effects of access recirculation. Both access recirculation and

rebound artifacts can be minimized by first slowing the blood pump to approximately 100 mL/min and then waiting ≥ 10 seconds but not > 20 seconds to draw the sample. To avoid haste and possible injury from needles used to draw the sample, the blood pump may be stopped after waiting the 10 – 20 second interval, and a sample drawn more leisurely from the arterial (dialyzer inflow) port. If access recirculation exists and the sample is drawn at full blood flow, the postdialysis BUN will be too low, giving the false impression that the patient is receiving more dialysis than is really the case; this will endanger the patient. If sampling is delayed too long (> 20 seconds after slowing the pump), the postdialysis BUN will be too high, in some cases giving the false impression of too little dialysis. Although this will not endanger the patient, it will cause inconvenience and inability to correlate dosage with outcome. If the blood tubing used in the dialysis center is the same from patient to patient, the volume of the tubing from the tip of the needle to the sampling port (usually 5 – 9 mL) can be measured. A volume of blood equivalent to 1.5 times this volume should be washed past the sampling port after slowing the blood pump and before sampling (e.g. if the volume is 8 mL, the pump can be stopped after seconds).

Troubleshooting

To measure dialyzer clearance and the patient's volume of urea distribution, blood flow rates must be accurate, but standard blood pump meters that rely on the pump's rotational speed (RPM) are subject to error. Imprecise calibration of the pump and low pre-pump pressures contribute to errors when *V* is measured on the blood side but not when *V* is measured on the dialysate side [19]. Conversely, when urea concentrations are measured on the dialysate side, proper calibration of the dialysate pump is essential. In addition to the causes of real reductions in dialyzer clearance listed in Table 6, an apparent reduction in clearance may be caused by overestimation of the dialyzer K_0A obtained from the manufacturer's specifications which may be based on saline dialysis instead of whole blood dialysis. False reductions in *V* or false elevations in G are encountered less often than their counterparts listed in Table 6. Modeled *V* may be too low if the postdialysis BUN is falsely low due to dilution as discussed above (*When to draw the post-dialysis BUN*). *V* may also be too low if the dialyzer K_0A is underestimated or if modeled dialysis time is less than the actual time. PCRn will be falsely elevated if either *V* or residual clearance is overestimated.

The Future

As HD equipment becomes safer to use and the treatment is better tolerated, the focus of development efforts will be turned more toward assuring adequacy. For intermittent dialysis as well as continuous dialysis, patient outcome ultimately translates to a sustained reduction in tissue levels of toxic solutes while the dialyzer effectiveness is essentially a measurement of clearance. Since we have not identified the key solutes to measure in the patient, we are left with measurement of dialyzer urea clearance, factored for body size, as a surrogate for this highly sought but currently unreachable goal. Medical science has hopes of uncovering the identity of the critical toxins and their mechanisms of toxicity that should help as a guide to more rational dialysis therapy in the future. Population studies may give

Table 6. Common Problems Uncovered by HD Urea Modeling

Potential causes of reduced clearance (high V)
– Malfunction of the blood or dialysate pump
  Low pre-pump pressure [19]
  Poor occlusion of pump head rollers
  Wrong blood pump segment
  Blood or dialysate pump calibration error
– Faulty dialyzer
  Clotting (inadequate anticoagulation during dialysis)
  Reused dialyzer, not terminated appropriately
  Channeling of blood or dialysate flow [41]
  Co-current rather than countercurrent flow of blood/dialysate
  Manufacturing variance
– Access recirculation
  Low access flow rate
    Peripheral A/V access: stenosis due to neo-intimal hyperplasia
    Central venous catheter access: short femoral catheter [40]
  Reversal of needles or catheters
  Close approximation of needle tips
– Blood sampling or measurement error (e.g. false elevation of post-dialysis BUN due to rebound)
– Error in timing: modeled time on dialysis greater than actual time
– Intradialysis parenteral nutrition (IDPN) causing transient elevation of G during dialysis [46]

Potential causes of low PCRn
– Low dietary intake of protein (anorexia, starvation, excessive protein restriction)
– Anabolic states
– False contraction of *V*
– Underestimation or failure to include residual clearance in the modeling
– Blood sampling or measurement error (e.g. drawing the predialysis BUN after starting the blood pump)

clues to the source and identity of toxic solutes and to resolve the question about appropriate denominators for normalizing the dose among patients at risk. The standards that are currently applied deserve continued scrutiny and refinement especially with regard to patients on the fringes of the normal distribution of known risk factors and perhaps others at risk from yet unidentified factors.

Because some of the answers to these questions are of national importance, the U.S. Division of Urologic and Hematologic Diseases (DKUHD) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) initiated a clinical trial, called the HEMO Project, in 1994 to examine and evaluate HD treatment regimens with the hope of reducing morbidity and mortality [23]. This study which will be completed in the year 2001, or perhaps before this if a significant benefit is seen, is designed to test the effect of dialysis dose and membrane porosity on patient outcome.

The more immediate future holds promise for expansion of dialysate methods, including real time feedback of dialyzer clearance, and other on-line technologies to guarantee the adequacy of each treatment. Recent concerns about the inefficiency of infrequent HD has underscored the advantages of daily dialysis. Technical advances in delivery systems on the horizon may allow HD to be administered more frequently with assistance from telemedicine and home monitoring.

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Renal Osteodystrophy

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It is well established that the kidneys play a pivotal role in maintaining mineral homeostasis and hormonal balance. Reductions in renal excretory and endocrine functions have a profound impact on divalent ion metabolism, calciotropic hormones, and thus on bone metabolism, resulting in renal osteodystrophy (ROD). The earliest histologic abnormalities of bone are seen after a relatively mild reduction in glomerular filtration rate (GFR) (creatinine clearances between 70 and 40 mL/min) [1]. Histologic changes are found in virtually all patients with end-stage renal failure (ESRD) [2].

The importance of renal bone disease extends beyond histologic, radiologic or biochemical abnormalities. Thirty years ago, it was reported that approximately 25% of patients with chronic renal failure (CRF) had symptomatic manifestations of ROD, such as bone pain and fracture and extraskeletal calcifications, with 10% of these presenting with severe symptoms [3]. With improvement in dialytic therapies, one could expect better control of divalent ions and bone homeostasis. However, adequate dialysis, per se, does not prevent the development of ROD [4] and while prolonging the life of uremic patients, long-term dialysis therapy is accompanied by more severe forms of ROD [3, 5, 6]. Indeed, more recently, it has been reported that bone pain was found in 36% and fractures in 10% of 259 dialysis patients [7]. Moreover, clinical manifestations of ROD, together with other long-term complications of dialysis, such as myopathy and amyloid bone disease, impact greatly the functional and psychosocial capacities of patients with ESRD and are responsible for a great part of morbidity and mortality. In a large study including 428 dialyzed patients, only 45% had normal physical activity scores [8] and in another survey, not more than one-third of the dialysis patients were considered able to work [9]. Since the incidence of ESRD in the United States is 68,870 patients/year (253/million/year) and the prevalence is 257,266 patients (967/million) [10], ROD is becoming a critical socioeconomic health problem.

ROD is not a uniform disease, and a large spectrum of systemic and histologic abnormalities can be observed, requiring different therapeutic approaches. Moreover, transformation from one form to another is not unusual [2]. Over the last decade, many factors have contributed to these changes, and correction of one abnormality can often lead to the aggravation of another. Bicarbonate dialysate became standard practice, calcium (Ca) salts replaced aluminum gels, and biocompatible membranes were introduced. Currently, dialysate Ca concentration is reduced and vitamin D metabolites are more widely used. Peritoneal dialysis (PD) is now an acceptable alternative to hemodialysis (HD). Finally, diabetic and aging patients comprise a large proportion of the dialysis population. These significant changes may have contributed to new trends seen in the spectrum of ROD [5, 11, 12]. These trends include the emergence, and

later decrease, in aluminum-related bone disease and the appearance of adynamic bone disease and β_2-microglobulin amyloidosis. Therefore, preventive or therapeutic approaches to patients with ROD remain an ongoing challenge for nephrologists [13].

A rational approach to the treatment of ROD requires a basic understanding of bone and divalent ion metabolism.

Functional Organization of Bone

The skeleton has a dual mechanical and metabolic function. The rigidity of the skeleton is responsible for maintenance of the human body configuration, protection of soft organs, and mobility through transmission of forces originated by muscle contraction. It is also the main reservoir for Ca, phosphate, and bicarbonate; thus, the skeleton contributes to the minute-to-minute regulation of extracellular fluid. Each bone consists of bone tissue, hematopoietic marrow, vasculature, and peripheral nerves. Bones from the axial skeleton include the skull, spine, thorax, and pelvis, whereas bones from the extremities comprise the appendicular skeleton. Pathologic processes and therapies can affect these skeletal sites in different ways [14].

Cortical and Cancellous Bone

Cortical or compact bone can be distinguished macroscopically from cancellous or trabecular bone. Cortical bone is a dense tissue that contains < 10% soft tissue. Cancellous or spongy bone is made up of trabecules shaped as plates or rods interspersed between bone marrow that represents > 75% of the cancellous bone volume. Cortical bone forms the external layer of all bones but is found predominantly in the appendicular skeleton, particularly in diaphysis of long bones. Cancellous bone is found mainly in the axial skeleton, located between the cortices of smaller flat and short bones such as scapulae, vertebrae, and pelvis. It is also present in limited amounts in the juxta-articular extremities of the appendicular skeleton. Cortical bone represents 80% of the skeletal mass and therefore supports most of the mechanical function [15]. Cancellous bone is only 20% of the skeletal mass but is metabolically 4 times more active per unit volume than cortical bone. Thus, the metabolic function is equally distributed between cortical and cancellous bones [15].

Bone Envelopes, Bone Surfaces, and Bone Structural Unit

The periosteal envelope represents the outer layer of connective tissue that encloses both hard and soft tissue and separates bone from other organs. The inner or endosteal envelope surrounds all soft tissue within the bone (except osteocytes) and is the boundary between soft tissue, mainly bone marrow, and bone tissue. Within the endosteal envelope, 3 distinct but continuous surfaces are observed: the intracortical, including the Haversian and Volkmann canals, the endocortical, and the trabecular surfaces. Modeling and remodeling activities take place on bone surfaces. However, the levels of activity vary from one surface to another and can be affected differently by physiological or pathological events as well as by therapeutic agents.

Between the periosteal and endosteal envelopes, bone is further organized in several structural elements, the bone structural units (BSU). The spatial arrangement of these smallest, individual units of bone and their cohesion are responsible for bone strength.

In cortical bone, BSU is represented by the osteon or Haversian system. Each osteon consists of a 200 – 250 μm wide cylinder running parallel to the long axis of cortical bone. The osteon center is occupied by a 40 – 50 μm "Haversian" canal containing blood vessels, nerves, and connective tissue. The Haversian canals of adjacent osteons are linked transversally by Volkmann canals, creating an intracortical network, which is also connected with the periosteum and bone marrow. The central Haversian canal is surrounded by concentric layers of 20 – 30 osseous lamellae, making the osteon wall approximately 70 – 100 μm thick. Osteons are densely packed and separated only by interstitial lamellae, which are the remains of incompletely resorbed osteons.

In cancellous bone, BSUs are flat and can be envisioned as longitudinally cut and unfolded osteons. They appear as semilunar packets roughly parallel to the central axis of the trabecule. The trabecular surface corresponding to the open Haversian canal follows the shape of the trabecule and is in contact with bone marrow. Within trabecules, the BSUs are separated from each other by interstitial bone, which, as in cortical bone, represents the remainder of older, incompletely resorbed packet.

Lamellar and Woven Bone

Each BSU consists of a specialized connective tissue, the osseous tissue, made of a mineralized protein matrix. At the microscopic level, 2 different types of bone can be identified by the arrangement of collagen bundles.

In the normal mature skeleton, bone is of the lamellar type. In this bone, the orientation of collagen fibers alternates regularly from layer to layer. Each layer is approximately 3 μm thick, with all collagen fibers deposited in the same direction. The deposited collagen exhibits an orderly lamellar pattern as circular layers alternating with longitudinal ones. The change in collagen fiber direction from layer to layer is responsible for the birefringence of bone under polarized light microscopy.

Contrasting with the regularity of lamellar bone, woven bone is composed of loose and randomly arranged collagen bundles. Woven bone is formed by irregular and unpolarized extrusion of protocollagen by osteoblasts. This matrix consists of an unordered, crisscross texture that lacks the birefringence typical of lamellar bone under polarized light. Woven bone is present in embryonic skeleton and in both cortical and cancellous bones during stages of rapid growth. After completion of bone growth, woven bone is replaced by lamellar bone in the normal skeleton. However, woven bone is also observed in certain pathologic conditions, such as Paget's disease of bone, fracture healing, osteogenesis imperfecta, and in primary or secondary hyperparathyroidism. In adults, woven bone is indicative of rapid, uncontrolled bone formation and high bone remodeling that is attributable to either local or systemic factors. It is of note that woven bone is inferior to lamellar bone in terms of mechanical properties.

Bone Cells

The Osteoclasts

Osteoclasts are large multinucleated cells located in resorption lacunae in the vicinity of

mineralized bone. Osteoclasts represent the main cells in the breakdown of bone matrix and bone mineral. They vary in size from 20 – 100 μm in diameter and usually display projections and lobes that give them an irregular appearance. Osteoclasts are highly mobile and go through cycles of resorption and rest. Thus, it is not surprising that these cells vary in histologic appearance, depending on the stage of the cycle at which they are observed. In normal skeleton, osteoclasts are somewhat larger than macrophages and may have from 2 – 5 nuclei. In pathologic states, osteoclasts are large, with up to 100 nuclei. The nuclei are found in the center of the cell. They are characteristically round or oval and usually contain 1 – 2 prominent nucleoli. Osteoclasts may appear mononucleated depending on the plane of the sections; however, serial sections may show other nuclei. These cells exhibit a characteristic pink staining with the modified Masson-Goldner trichrome stain due to abundance of mitochondria, lysosomes, and ribosomes in their cytoplasm. Their foamy appearance reflects the presence of numerous endocytic and lysosomal vacuoles. The ruffled border, the ultrastructural trademark of osteoclasts, consists of numerous foldings of the apical membrane and is occasionally identified at high magnification on thin histologic bone sections. However, in the majority of bone samples, the ruffled border is not recognizable.

The Osteoblast Lineage Cells

Osteoblasts are mononucleated cells responsible for production of bone matrix and are involved in its mineralization. Under light microscopy, mature osteoblasts in normal bone form a monolayer of cells in front of the bone formation site. They are cuboidal, polarized cells measuring between 15 – 25 μm in diameter. Their round nuclei are located at the basal pole of the cells (away from bone) and contain one or more nucleoli. The cytoplasm is strongly basophilic due to the large amount of endoplasmic reticulum and Golgi apparatus responsible for active production of type I collagen and other substances found in the bone matrix. Osteoblasts at a bone formation site give the appearance of an epithelium-like organization. They exhibit gap junctions that ensure their cohesion and provide cell-to-cell communication. During active bone formation, osteoblast cells are plump. Towards completion of the new bone packet, the osteoblast shape flattens, its cytoplasm loses its basophilic characteristics, and its nuclei become elongated. The majority of these resting osteoblasts become bone-lining cells observed above the quiescent surfaces.

Also, approximately 10% of osteoblasts turn into osteocytes, that is, they become embedded in the bone matrix before its mineralization and become stellar cellular complexes with a central nucleus and numerous long cellular processes. Gap junctions have also been described between the peripheral processes of osteocytes, osteoblasts, and bone lining cells from the same bone area. When matrix mineralizes, osteocytes are found in osteocytic lacunae, the border of which has been found to be calcified by osteocytes. Long cytoplasmic processes are seen in canaliculae. Newly embedded osteocytes conserve the cellular characteristics of osteoblasts, and the oldest ones in deeper bone area lose signs of protein synthesis and accumulate glycogen. The periosteocytic space between osteocytes and mineralized bone contains the bone extracellular fluid (1 – 1.5 L), and the bone-lining cell/osteocyte network plays an important role in the minute-to-minute Ca homeostasis as the osteocytes are rapidly exposed to changes in circulating factors. Due to their deep location in mineralized bone, osteocytes

are also considered sensors for fatigue damage and microfractures and thus may represent an important contributor to the regulation of bone remodeling and bone turnover.

Bone Marrow Cells

Besides bone cells, other cells are present in the bone microenvironment. There is ample evidence that bone marrow cells play a role in the local regulation of bone remodeling and bone turnover. Cells from the monocyte-macrophage and lymphoid lineages produce various substances such as cytokines and growth factors that directly or indirectly act on bone cell recruitment and activity [16]. Moreover, macrophages have the capability to produce calcitriol [17, 18]. Mast cells, which produce heparin, a proven stimulator of bone resorption, may also be involved in the local regulation of bone [19, 20].

On bone biopsy samples, it is common to observe that states of high bone turnover are often associated with various degrees of bone marrow cell hyperplasia, whereas low-turnover states of bone are accompanied by variable hypoplasia of hematopoietic cells [2].

Bone Modeling and Remodeling

During life, the skeleton is not static but undergoes numerous transformations. First, there is growth, also called bone modeling, when the overall shape and size of bones change. The 2 types of bone growth are longitudinal and appositional modeling. Longitudinal growth occurs by enchondral ossification, a process that takes place at the growth plate, when cartilage proliferates and progressively calcifies creating new trabeculae until the epiphyseal growth plate fuses. Appositional modeling, i.e. the growth of bone in width, proceeds by periosteal apposition of new bone and endosteal resorption of old bone.

After epiphyseal growth plates close, the adult skeleton continues to renew itself without noticeable changes in macroscopic shape. This is bone remodeling. The primary function of bone remodeling is to replace old bone with new bone. Old bone contains high mineral density and microfractures that decrease its mechanical properties. Approximately 3% of cortical bone and 25% of cancellous bone are renewed per year in the mature human skeleton [21]. Bone remodeling occurs in distinct locations on bone surfaces, the bone remodeling units (BRUs) [15]. BRUs require the involvement of a team of different cells, the bone multicellular units (BMUs). The remodeling of a “packet” or “quantum” of bone entails sequential events known as the remodeling cycle. This remodeling cycle includes activation, resorption, reversal, formation, and quiescence.

The signaling factors responsible for the initiation of the remodeling cycle are not well understood. Structural and/or biomechanical characteristics of old bone packets may play a role in this early phase, and signals may be relayed through the osteocyte-lining cell system to osteoblasts and bone marrow cells [15]. Numerous factors known to stimulate bone resorption are probably involved in the activation of bone remodeling that also requires interaction between hormones, cytokines, and growth factors and their receptors in bone cells and bone marrow cells. Activation of bone surface is accompanied by mobilization of mononucleated osteoclast precursors, retraction of the lining cell layer, and exposure of bone matrix chemotactic substances such as osteocalcin, osteopontin, transforming growth factor β (TGFβ), and type I collagen [22 – 29].

The progressive fusion of mononucleated osteoclast precursors results in a team of 1 – 4 mature, active, and multinucleated osteoclasts at each remodeling site. The team of osteoclasts then adheres to bone surface along a ring, i.e. the sealing zone, leaving an extracellular bone-resorbing compartment, and then bone resorption begins. Osteoclasts dissolve bone mineral through acidification of the subosteoclastic compartment. This process involves proton pumps and carbonic anhydrase. Bone matrix is hydrolyzed by proteolytic enzymes such as collagenase. Osteoclasts are motile cells and move along the erosion cavity. They are responsible for the rapid resorption (~ 7 days) of two-thirds of the final eroded cavity. Mononucleated cells resorb the other one-third at a slower rate (~ 36 days) [30]. These mononucleated resorbing cells consist of either unfused original osteoclast precursors or segmentated osteoclasts. The rapid osteoclastic resorption leaves behind a rather rough surface that is transformed by the mononuclear cells into a smooth bone surface. In cortical bone, the resorption process takes place along the long axis of bone, and osteoclasts are observed in the cutting cone with depths reaching 100 μm. In normal cancellous bone, osteoclasts erode bone parallel to the bone surface, forming a shallow cavity with a depth of 40 – 60 μm.

After resorption ceases, there is a transition period before bone formation occurs, i.e. the reversal phase. During this 1-to 2-week phase, a layer of material with particular optical characteristics is deposited at the bottom of the resorption lacunae. On histologic section this line is positive for acid phosphatase staining and presents with a different birefringence under polarized or phase contrast light microscopy. This line (surface) serves as a cement or glue between old and new bone to be apposed and is referred to as the reversal or cement line. Only mononucleated cells are seen in front of the resorption lacunae during this phase and probably are responsible for the deposition of cement line. The exact origin of these cells is not known. Concurrent with the reversal phase, other events take place that are responsible for the coupling between resorption and formation. In the adult skeleton, bone is formed only on a previously eroded surface. This implies that signals are emitted to promote osteoblast proliferation and to direct osteoblast precursors to a precise location on the bone surface. The complex mechanisms responsible for this coupling phenomenon are not fully understood. However, several local agents such as chemotactic substances, growth factors, and cytokines are probably involved in this event.

After differentiation, osteoblasts form a layer in front of the reversal lacunae and deposit matrix protein, i.e. osteoid. Mineralization of osteoid seam starts 5 – 15 days later when the osteoid seam is approximately 20 μm thick. Apposition of osteoid is rapid at first, then progressively slows down. The mineral apposition rate follows the same pattern. First, osteoid is mineralized at a rate of 1 – 2 μm/day and subsequently slows down but is still faster than matrix apposition at that time. When matrix apposition ceases, the remaining layers of osteoid are slowly mineralized. The first hydroxyapatite crystals are small and immature, and therefore Ca ions can chelate other substances present at high concentration in the bone microenvironment. These substances may include aluminum, fluoride, and others, in particular tetracycline hydrochloride. Under fluorescent light microscopy, deposits of tetracycline in new bone are spontaneously visible on unstained sections and appear as bright yellow bands. The technique of tetracycline double labeling (discussed later) uses this phenomenon to determine the rate of mineralization. However, when tetracycline is administered, it chelates reversibly to all ex-

posed bone surfaces, i.e. resorptive cavities and at the mineralization front. Therefore, it is necessary to perform a bone biopsy within a few days after the last administration of the antibiotic, usually 2 – 4 days. This ensures that the tetracycline chelated at the mineralization front is protected from leaching out by a thin layer of newly mineralized bone. During bone formation, osteoblasts are first cuboidal and very active, then they flatten and become lining cells when the osteoid seam is completely mineralized. Moreover, a certain fraction of osteoblasts is embedded in bone matrix and becomes osteocytes (see above). Also, some osteoblasts may locally undergo apoptosis [31]. The total duration of the bone formative phase in normal skeleton is approximately 3 months.

A phase of quiescence follows. During the beginning of this phase (3 – 6 months), the newly formed "young" bone packet will mature by increasing its mineral density. New bone is separated from bone marrow by the layer of lining cells and a thin collagenous membrane. In normal adult bone, the majority of bone surface is in a quiescent stage (80%).

Bone Balance and Bone Turnover

In normal young adults, coupling between the amount of bone resorbed by osteoclasts and the amount of bone formed by osteoblasts results in bone balance. Uncoupling between formation and resorption will result either in negative or positive bone balance at the remodeling site. In states of negative bone balance, the amount of bone resorbed is disproportionately higher than bone formed; conversely more bone is deposited than resorbed when bone balance is positive.

If bone remodeling represents the cellular-based events that occur at a specific site of the bone surface, bone turnover represents the rate at which the skeleton is renewed. This depends on the activation rate and the extent and distribution of the remodeling sites among the various bone envelopes. If bone turnover is high, the minute changes observed at the bone remodeling sites are amplified. For example, in case of negative bone balance, bone loss is greater in individuals with high bone turnover, and reduction of turnover will result in slower bone loss.

In bone biopsies, it is common to observe that states of high bone turnover are often associated with various degrees of bone marrow cell hyperplasia, whereas low-turnover states of bone are accompanied by variable hypoplasia of hematopoietic cells [2].

Role of Bone in Calcium and Phosphate Metabolism

Bone has an important role in mineral and acid-base homeostasis. Bone possesses 2 fundamental properties that greatly facilitate this function. First, there is the enormous capacity of the apatite crystals and the calcium phosphate salts to adsorb bone-seeking elements such as Ca, phosphorus (Pi), magnesium, aluminum, and zinc. Second, the large skeletal surface between the osteocyte-lining cells network and the extracellular fluid compartment facilitates ion exchange. Besides facilitating mineral movement in and out of bone, these highly complex anatomical arrangements contribute to the metabolic and electrical coupling of bone cells.

Bone is considered the largest primary Ca reservoir of the body, and it plays a major role in Ca homeostasis. The extracellular Ca concentration is determined by the rates of Ca entry into and loss from the extracellular fluid. Ca enters the extracellular space via 3 routes:

intestinal absorption, which is the major contributor to the available Ca pool, Ca release from bone and renal tubular reabsorption. Ca loss occurs by means of gastrointestinal digestive juices, bone uptake during mineralization and urinary loss.

There is a daily flux of approximately 110 nmoles of Ca into and from the bone [32]. Only 10% of this Ca is exchanged through remodeling surfaces [32]; the rest is transferred across the quiescent surfaces of bone and bone lining cells. The exact cellular mechanism(s) that influence Ca fluxes across this bone membrane are poorly understood. However, there is considerable evidence to suggest that parathyroid hormone and calcitriol, individually or synergistically, play an important role in governing Ca translocation across bone surfaces, independently of their role in bone remodeling [32].

The Role of Bone in Acid-base Homeostasis

It has long been recognized that bone mineral contributes to the buffering mechanisms in acute and chronic acidosis [33 – 35]. It appears that both low pH and low bicarbonate concentration independently influence Ca flux from bone [36]. Current evidence indicates that short-term acidosis mainly influences the physicochemical solution equilibria, while long-term acidosis affects Ca efflux via the activation of bone resorption mechanism [36].

Factors Affecting Bone Metabolism

It is increasingly apparent that bone cells are regulated by a complex interplay between systemic hormonal signals and local factors [37]. Bone cells are influenced by systemic factors and various circulating blood cells, particularly leukocytes that reach bone via capillary circulation. Bone cells are also in close proximity to local cells such as endothelial cells, chondrocytes and stromal (hematopoietic) cells that are capable of responding to circulating substances as well as secreting their own growth-regulating factors. It is only for simplification and practicality that one can categorically separate circulating factors from local factors.

Circulating Factors

Parathyroid Hormone (PTH)

PTH, an 84 amino acid polypeptide, is synthesized in a precursor form, pre-pro-PTH of 115 amino acids. Post-translational cleavages yield a 90 amino acid polypeptide (pro-PTH) and then the active 1-84 PTH, which is stored within intracellular secretory granules [38]. In the absence of a stimulus for PTH release, partial or complete intracellular degradation of the hormone to smaller polypeptide fragments or to its constituent amino acids may occur [39]. For example, a significant proportion of the immunoassayable hormone is secreted in the COOH-terminal fragment form during hypercalcemia [40]. The half-life of intact 1-84 PTH is short (< 10 minutes) due to effective enzymatic cleavage in the liver

(Kupffer cells) and the kidney (tubular cells) [41 – 43]. An important initial cleavage is around position 35, yielding to the bioactive 1-34 NH2-terminal and the bioinactive COOH-terminal, which has a longer half-life (1 – 2 hours) and is excreted by the kidney. Therefore, the kidney plays an important role in PTH metabolism, both by glomerular clearance of C-terminal fragments and by tubular degradation of intact PTH.

Intracellular cAMP is an important modulator of PTH secretion. Factors that increase cAMP accumulation (β-adrenergic catecholamines, dopamine, secretin, prostaglandin E2, glucagon, vasoactive intestinal peptide and histamine) all stimulate PTH secretion. Conversely, agents that inhibit cAMP accumulation in parathyroid cells such as Ca, α-adrenergic catecholamines, and prostaglandin F2α, also inhibit PTH secretion [44, 45]. Extracellular ionized calcium concentration [Ca^{2+}] is the principal regulator of PTH release. Many studies have documented a steep inverse sigmoidal relationship between the extracellular [Ca^{2+}] and PTH secretion [46], in which a minimal reduction of 0.1 – 0.2 mg/dL of [Ca^{2+}] represents a significant stimulus to PTH release [47]. A parathyroid calcium-sensing receptor was long suspected [46]. However, it was not until recently that such a receptor was isolated and characterized [48]. The Ca receptor is linked to several intracellular second messenger systems by guanine nucleotide regulatory (G) protein [46]. Some of the intracellular effects of the Ca receptor agonists include the inhibition of cAMP accumulation, the accumulation of inositol triphosphate (IP3), with the resultant increase in intracellular Ca concentration, and the inhibition of protein kinase C [46]. Exactly how these intracellular events lead to the inhibition of PTH secretion is uncertain. Recently, Okazaki et al. described a negative calcium-responsive element located upstream of the PTH gene and regulated by extracellular Ca concentration [49].

Accumulated evidence suggests that PTH secretion follows a circadian rhythm, with peak levels in the late evening hours [50, 51]. Furthermore, broad pulsatile secretion patterns were observed to occur approximately each hour [50, 52]. It has also been recognized that the rate and direction of the changes in Ca concentrations, in addition to the absolute extracellular Ca concentration, are important in modulating PTH secretion. For example, at any given low Ca concentration, the PTH level would be higher if measured during induction of hypocalcemia than if measured during the recovery of a hypocalcemic state. This phenomenon is termed hysteresis [53, 54].

In vitro studies show that magnesium appears to parallel the effect of Ca on PTH release, although with reduced efficacy [55, 56]. However, in vivo studies show that chronic severe hypomagnesemia impairs PTH secretion and reduces its end-organ effects [57 – 59]. Hyperphosphatemia is associated with increased circulating levels of PTH in renal failure. This effect is, in part, secondary to the associated hypocalcemia that accompanies elevated Pi levels [60]. However, a recent preliminary study by Silver et al. demonstrated a direct effect of Pi on the secretion of PTH messenger RNA (mRNA) in vitro [61].

Parathyroid cells possess vitamin D receptors and are capable of localizing injected radioactive 1,25-[H3]-dihydroxyvitamin D [62]. It is now apparent that 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) has multiple direct effects on parathyroid glands that include: inhibition of PTH synthesis and secretion [63, 64], reduction in parathyroid cell proliferation [65], and possibly facilitation of cell death by apoptosis [66]. Conversely, PTH exhibits a positive effect on 1-α hydroxylase, a tightly regulated enzyme in the production pathway

of $1,25(OH)_2D$ [67]. These observations explain the elevated circulating levels of $1,25(OH)_2D$ found in patients with primary hyperparathyroidism [68]. The interactions between PTH and $1,25(OH)_2D$ form the basis of a feedback loop that has an important role in the pathogenesis of secondary hyperparathyroidism in patients with renal failure.

The major role of PTH is to tightly regulate extracellular Ca concentration and keep it within narrow limits. This function is achieved by exerting important direct actions on bone and kidney and indirect effects on the intestine. Receptors for PTH have been recently cloned and characterized in opossum kidney, rat osteoblasts, and human kidney cells [69 – 71]. Parathyroid hormone interacts with these specific membrane-bound receptors to initiate a cascade of intracellular events that involve protein G activation with resultant cAMP generation, phosphatidylinositol and Ca transport activation [72].

Effects of PTH on Bone

PTH maintains extracellular Ca concentration by facilitating Ca fluxes from and to the skeleton. Osteoblasts and cells of osteoblastic lineage (the lining cells and osteocytes) are the only cell type in bone found to possess PTH receptors [73 – 76]. It appears that Ca movements from bone proceed in at least 2 phases. First, there is a rapid mobilization from the lining cells and osteocytes as evidenced by the prompt structural response of these cells to injected PTH [77] as well as the rapid release of radiolabeled Ca from bone surfaces following PTH administration [78]. Secondly, there is a slow (hours) response that is dependent on mineral release by osteoclasts during bone resorption [78]. One of the most recognized effects of PTH on bone is the enhancement of osteoclast activity and numbers [79]. This effect is, in fact, dependent on osteoblast activation since, in vitro, osteoblasts are required for PTH control of bone resorption [74, 80] and osteoblasts release factor(s) that stimulate bone osteoclastic resorption [81, 82]. However, most recently Langub et al. (submitted) were able to show PTH/PTHrP receptors in osteoclasts of bone biopsies from normal human individuals and patients with renal failure.

In vivo, PTH increases not only osteoclastic resorption but also osteoblastic anabolic activity. In vitro, however, PTH inhibits osteoblast activity [83]. This apparent discrepancy can be related to differences in dosages or to the intermittent and pulsatile secretion of PTH in vivo, as opposed to the continuous effect in vitro [83, 84]. Under physiological conditions, these synchronized anabolic and resorptive actions of PTH contribute to the maintenance of skeletal balance, which can be markedly disturbed in hyperparathyroidism.

Effects of PTH on the Kidney

In order to maintain Ca homeostasis, PTH enhances fractional absorption of Ca in the thick ascending loop of Henle and in the distal tubule [85, 86]. PTH also enhances phosphate secretion by inhibiting phosphate reabsorption in the proximal as well as the distal tubules [87 – 90]. During hypocalcemia, this phosphaturic effect of PTH facilitates the disposal of the large phosphate load that is invariably coupled to Ca mobilization from bone.

Another important renal action of PTH is its influence on the production of $1,25(OH)_2D$, the active metabolite of vitamin D. As discussed above, PTH directly activates 25(OH)D-1α-hydroxylase found in proximal tubular cells leading to an increase in $1,25(OH)_2D$ production [67]. Finally, PTH also inhibits proximal bicarbonate reabsorption [88]. This effect is usually minor at physi-

ological concentrations of the hormone or is overridden by other homeostatic mechanisms. However, it is not unusual to see systemic acidosis in hyperparathyroidism secondary to urinary bicarbonate losses [44].

Other Effects of PTH

PTH administration leads to an increase in intestinal Ca absorption, an effect related to the increase in vitamin D production. In the liver, PTH undergoes degradation and enhances gluconeogenesis. Recently, Tian et al. observed the presence of PTH receptor mRNA in many tissues other than the kidney [90], including the liver, heart, brain, testis, spleen, lung and skeletal muscle. The role of PTH in these organs is not yet entirely clear. Langub et al. (submitted) demonstrated PTH/PTHrP receptor message in human osteoblasts, ostecytes, and osteoclasts.

Vitamin D

Vitamin D molecules are fat-soluble steroids known to have a protective effect against rickets [91]. It is only in recent years that modern molecular techniques have uncovered remarkable findings that have substantially augmented the role of these hormones. It is now recognized that the most biologically active vitamin D metabolite, calcitriol ($1,25(OH)_2D_3$) binds to a cytoplasmic vitamin D receptor (VDR). The vitamin D-VDR complex subsequently binds to nuclear DNA and alters a variety of transcriptional genes [92]. VDR have been found not only in the conventional target organs for vitamin D such as the intestine, the kidney and bone; but also in a number of diverse tissues: parathyroid glands, pituitary gland, ovaries, skin, hair follicles, stomach, pancreas, thymus, breast, peripheral leukocytes, cardiac and skeletal muscles, and tumor cell lines, among others [92 – 98]. The physiological and clinical implications of these newly discovered functions of vitamin D are exciting and hold tremendous potential.

In humans, there are 2 major sources for vitamin D. One is through the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D_3) by the effect of sunlight on the skin. The other is through the intestinal absorption of both vitamin D_3 from animal sources and ergocalciferol (vitamin D_2) synthetically produced by ultraviolet irradiation of plants or fungal ergosterol. Since sun exposure can vary widely and few food products contain vitamin D, many countries throughout the world now employ dietary vitamin D supplementation. Once vitamin D (D refers to D_2 and D_3) reaches the circulation from the skin or via the lymphatic thoracic duct, it binds to an α2-protein, vitamin D-binding protein (DBP), which transports the vitamin primarily to the liver and body fat pools [99]. Adipose tissue and the large proportion of the unbound DBP (> 95% of its binding capacity) provide a large pool for vitamin D that protects against excess vitamin D intake or skin production [100, 101]. In the liver, vitamin D is hydroxylized, by the enzyme 25-hydroxylase, to 25-hydroxyvitamin D (25-(OH)D). This is the most abundant form of vitamin D [102, 103]. It is 2 – 5 times more active than vitamin D itself [104]. The normal plasma concentration of 25-(OH)D is 10 – 40 ng/mL and its half-life is estimated to be approximately 15 days. In contrast, parent vitamin D has a normal plasma level of 1 – 2 ng/mL and its half-life approaches 30 days.

To exert its full range of biological activities, 25-(OH)D requires further metabolism in the kidney [105] by 25-(OH)D-1α-hydroxylase, a tightly regulated enzyme located mainly in the proximal tubules. This enzyme

converts 25-(OH)D to 1,25-$(OH)_2$D [106, 107] which is approximately 10 times more potent than its parent vitamin D [104]. Normal plasma concentration of calcitriol is 15 – 60 pg/mL and its half-life is only 5 hours [44]. 1α-hydroxylase enzyme is regulated by a variety of factors that maintain a highly controlled calcitriol production. Hypocalcemia, with the resultant increase in PTH plasma levels, enhances calcitriol production [108, 109] in order to correct the Ca deficit. In vitro, low Pi is a direct stimulus to 1α-hydroxylase [110], and in humans hypophosphatemia stimulates calcitriol production [111]. Vitamin D monitors its own production. In states of vitamin D deficiency, there is a marked increase in 1α-hydroxylase activity [112] while in states of calcitriol excess 1α-hydroxylase is inhibited [93]. When Ca demands are increased, for example during pregnancy, lactation, or skeletal growth, there is an enhancement of calcitriol production probably through the direct or indirect effect of estrogen, prolactin, or growth hormone [105, 113]. It is known that the kidney is the main source of 25(OH)D-1α-hydroxylation. However, other organs such as the placenta or granulomatous tissues may contribute to 1,25-$(OH)_2$D production [105]. Furthermore, 1,25-$(OH)_2$D is synthesized and utilized locally at the bone cellular level [114 – 116].

In the kidney, 25-(OH)D can also be metabolized by 24-hydroxylase, which results in 24,25-$(OH)_2$D, an inactive metabolite [117]. This metabolite is the most abundant dihydroxyvitamin D in the serum (100 times the concentration of calcitriol) [44]. Its production is activated by calcitriol [117, 118]. Therefore, excess calcitriol leads to inhibition of 1α-hydroxylase in order to reduce calcitriol production and to prevent hypercalcemia; and activation of 24-hydroxylase in order to enhance 25-(OH)D conversion to an inactive metabolite.

Actions of Vitamin D

An important function of vitamin D is to enhance Ca and Pi absorption in the gut [93, 119]. The exact mechanism by which vitamin D increases Ca absorption is not yet well known. It could involve the production of several intestinal proteins that may serve as Ca carriers across the plasma membrane, through the cytoplasm of intestinal cells, and across the basolateral membrane [93, 105]. In mammals, vitamin D enhances the production of a calcium-binding protein (CaBP), calbindin D9k, which contains 2 domains that bind Ca with high affinity [44]. There is a close association between the appearance of this protein and the induction of Ca absorption [93], which indicates its possible role as a Ca carrier. Calbindin D9k may also play a role as an intracellular Ca buffer [120]. Vitamin D also stimulates phosphate absorption [93]. No carrier for phosphate is identified, and the exact mechanism by which vitamin D enhances phosphate transport is yet to be clarified [93].

Effects of Vitamin D on Bone

It is well known that vitamin D deficiency leads to rickets or osteomalacia [93]. Therefore, the role of vitamin D in bone mineralization has been suspected. Evidence from rat studies suggests that vitamin D indirectly affects mineralization through maintaining normal serum Ca and Pi levels [93, 121]. However, we have demonstrated in dogs, which have skeletons more akin to humans, that vitamin D is required, in addition to normal Ca and Pi concentrations, for adequate mineralization [122]. In vitro, vitamin D has a direct resorptive effect on bone [123]. It also stimulates Ca mobilization from the bone fluid compartment to the extracellular space [93]. In vivo, however, the direct resorptive effect of vitamin D is shown only in hypocalcemic conditions or states of vitamin D deficiency.

There is also significant evidence to suggest that the effect of PTH on bone is facilitated by vitamin D [124, 125].

Renal Effects of Vitamin D

The exact role of vitamin D in renal handling of Ca and Pi remains unclear. In part this is due to its interaction with other hormones, particularly PTH, that might lead to synergistic or antagonistic effects [126]. Vitamin D increases tubular phosphate reabsorption, an effect that can be attributed to PTH suppression [127]. The effect of vitamin D on renal Ca handling is also suggestive of a tubular Ca reabsorptive effect [128]. As indicated above, 1,25-$(OH)_2D$ inhibits renal 1α-hydroxylase and activates 24-hydroxylase [106, 107, 117].

Other Effects of Vitamin D

Recently, diverse effects of vitamin D have been described. As discussed above, vitamin D directly inhibits PTH production, PTH secretion, and parathyroid cell proliferation [63 – 65]. Vitamin D also inhibits the proliferation of cultured melanoma cells, fibroblasts, and keratinocytes [129 – 131]. There is evidence to suggest that vitamin D enhances cell differentiation and inhibits cell growth [95, 132, 133]. Finally, by affecting lymphocytes, vitamin D may play a role as an immunoregulatory hormone [134, 135]. These effects of vitamin D are the result of its role in regulating a large number of genes upwards or downwards.

Calcitonin

Calcitonin, a 32-amino acid peptide, is secreted by the parafollicular cells of the thyroid gland. Its main action is to inhibit osteoclast resorption activity via a cyclic AMP (cAMP)-mediated mechanism [136]. The antiresorptive effect is quite rapid and evident at the physiological concentration of the hormone [136]. The calcitonin hypocalcemic effect is probably related to its antiresorptive activity [44] and usually is not evident unless a state of high bone turnover is present [137]. In other words, calcitonin does not induce hypocalcemia in normal subjects [138]. Many factors affect calcitonin secretion, the most important of which is hypercalcemia [139]. Other factors include gastrin, cholecystokinin, and probably estrogen and calcitriol [137]. Calcitonin gene-related peptide (CGRP) is another peptide encoded by the calcitonin gene. Like calcitonin, this hormone has similar action on osteoclasts, but it might also have a PTH-like effect on osteoblasts [137]. The physiological role of this peptide in bone remodeling may be related more to its local abundance at the bone level rather than as a circulating hormone [137].

Other Circulating Factors

Other hormonal factors such as thyroid hormone, estrogen, testosterone, and glucocorticoid have an impact on bone metabolism [140]. Also, vitamins A, C, and K all play a role in maintaining normal bone metabolism. Hypovitaminosis A may lead to inhibition of bone resorption and enhancement of bone formation [141]. Vitamin C is required for the hydroxylation of proline and lysine, an essential step in the synthesis of bone matrix collagen [142]. Finally, vitamin K is required for the synthesis of many proteins including osteocalcin, a protein that may play a role in bone mineralization [143] and Ca homeostasis [144].

Local Factors

It is increasingly apparent that the highly coordinated process of bone remodeling depends on the production of local substances [37]. PTH stimulates osteoblasts to produce local coupling factors involved in the activation of osteoclasts [81]. It is also possible that the timing of the end of resorption and the initiation of bone formation in the remodeling cycle are controlled by local signals. A number of growth factors are involved in the local control of bone remodeling. These factors are synthesized by skeletal cells or by cells from adjacent tissues (cartilage, marrow cells) [145]. In vitro, insulin-like growth factors (IGF-I and IGF-II) were shown to stimulate bone cell proliferation and collagen synthesis. In vivo, transforming growth factor β (TGFβ) was shown to enhance bone formation [146, 147]. TGFβ also stimulates bone resorption, probably by enhancing prostaglandin production [148]. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are stimulators of bone resorption [149, 150]. Recently, it was shown that IL-6 and IL-11 production can be regulated by PTH [151 – 153]. This adds further evidence of the importance of the interplay between systemic and local factors.

Pathogenesis of Renal Osteodystrophy

With the progressive loss of excretory kidney function, abnormalities in divalent ions and secondary hyperparathyroidism typically develop early on.

Factors Implicated in the Development of Secondary Hyperparathyroidism

In advanced renal failure a variety of factors have been identified as direct stimulators of PTH secretion. They include hypocalcemia, low circulating calcitriol (the active vitamin D metabolite), and, more recently, hyperphosphatemia. However, most patients with mild chronic renal failure exhibit increased serum PTH levels without alterations in serum levels of Ca, Pi, and calcitriol.

Early Renal Failure

The early sequence of events is still not fully elucidated. However, the early stages of renal failure are marked by some signs of end-organ resistance to vitamin D, such as mild decrease in intestinal Ca absorption and altered calciuric response to oral (PO) supplementation of calcitriol. Calcitriol exerts its action by binding to VDR, which interact with specific sequences of nuclear DNA, the vitamin D response elements (VDRE) that control genomic synthesis of many proteins, including PTH. In early renal failure, the binding of the hormone-VDR complex to VDRE has been found to be reduced, which could lead to less suppressive effects of physiologic blood levels of calcitriol on PTH synthesis, and therefore PTH overproduction [154]. The exact mechanisms implicated in the impaired binding of hormone-VDR complex to VDRE are not fully elucidated. In experimental rats, alterations in the VDR heterodimer partner, retinoid X receptor (RXR), have been observed; however, this has not been proven in humans. Other alterations in accessory nuclear factors, abnormal phosphorylation, and conformation of VDR or chemical alteration

of the DNA binding domain may be involved in the impaired VDR response to calcitriol.

Advanced Renal Failure

With more advanced nephron loss, phosphate load of the remaining functioning nephrons progressively increases. This results in inhibition of C_1-α-hydroxylase, the enzyme responsible for the conversion of 25-hydroxy vitamin D to its active metabolite, 1,25-dihydroxy vitamin D (calcitriol). Calcitriol deficiency in turn further decreases intestinal Ca absorption, resulting in hypocalcemia. Calcitriol deficiency in advanced renal failure is associated with a decreased number of VDRs, in particular in parathyroid glands. Since calcitriol has been shown to suppress the expression of pre-pro-PTH mRNA, lower circulating calcitriol levels together with a low number of VDR in patients with ESRD result in stimulation of both PTH synthesis and secretion. Low blood Ca^{2+} levels rapidly stimulate PTH secretion, whereas high Ca concentrations suppress it. The relationship between Ca^{2+} and PTH follows a sigmoidal pattern. The action of Ca on parathyroid gland cells is associated with modulation of intracellular cyclic AMP. The short-term stimulation induced by low Ca is due to release of stored preformed hormone and an increase in the number of cells that secrete PTH. More prolonged hypocalcemia induces changes in intracellular PTH degradation with reutilization of degraded hormone and mobilization of secondary storage pool. Within days or weeks of the onset of hypocalcemia, pre-pro-PTH mRNA expression is stimulated. This effect is exerted through a recently described negative calcium-response element located in the upstream flanking region of the PTH gene. Ca exerts its effects on parathyroid gland cells through a recently isolated G-protein-coupled calcium-sensing receptor located on the cell membrane. The expression of the Ca receptor has been shown to be suppressed by calcitriol deficiency and stimulated by calcitriol administration, suggesting an additional regulatory mechanism of the active vitamin D metabolite on PTH production. The decreased number of calcium-sensing receptors with low circulating calcitriol may, at least in part, explain the relative insensitivity of parathyroid gland cells to Ca in patients on dialysis (higher set point).

When GFR reaches levels of < 25% of normal, serum Pi levels rise. At this level of reduced renal function, the ability of the remaining nephrons to increase phosphate excretion is exhausted. Increased serum Pi levels further decrease serum Ca through physicochemical binding and suppress the C-1α-hydroxylase activity, resulting in further lowering of circulating levels of calcitriol. Moreover, a direct stimulatory effect of Pi on parathyroid gland cells, independent of Ca and calcitriol, has been recently observed in ESRD patients. The mechanism of the direct action of Pi on PTH secretion is not fully elucidated.

All the mechanisms described above result in increased production of PTH and increased parathyroid gland mass. The size of the parathyroid glands progressively increases with time in dialyzed patients and parallels serum PTH levels. This increase in size is mainly due to cellular diffuse hyperplasia. Patients may also develop monoclonal cell growth resulting in the formation of tumor-like nodules that have less or no VDR and calcium-sensing receptors and that promote parathyroid gland resistance to calcitriol and Ca.

Factors Affecting PTH Production and Its Effects on Bone

Other systemic factors such as α-adrenergic agonists, dopamine, prostaglandin E, secretin, and phosphodiesterase inhibitors that alter the cyclic AMP content of parathyroid cells may increase PTH secretion. Recently, the inflammatory cytokine IL-8 has been found to stimulate PTH secretion. The effect of magnesium in regulating PTH secretion is similar to that of Ca but not as potent. Moreover, there is reduced peripheral degradation of PTH in uremia, and numerous PTH fragments circulate, thus prolonging the effects of PTH on target organs.

Accumulation of aluminum in bone and other organs such as the parathyroid glands may occur in patients on dialysis or before initiation of dialysis. Aluminum accumulation in the parathyroid glands results in decreased secretion of parathyroid hormone and suppression of bone turnover. In addition, aluminum inhibits renal and intestinal C1-α hydroxylase activity and may thus further contribute to reduced levels of calcitriol. Possible sources of aluminum include high concentrations in water used for dialysis, prescription of aluminum-containing phosphate binders, and aluminum in drinking water, infant formula, and other liquids or solid food.

Bone is an important buffer for excess acid production in patients with ESRD. Metabolic acidosis has been shown to stimulate bone resorption and to suppress bone formation, resulting in negative bone balance.

Patients with ESRD are in a hypogonadal state, and some of them are treated with glucocorticoids, which have an impact on bone metabolism. Patients on chronic dialysis present with retention of β_2-microglobulin and alterations in cytokines, growth factors, PTH, and VDR that may be involved in the regulation of bone remodeling, thus affecting the histologic pattern of renal osteodystrophy.

Histological Spectrum of ROD

Renal osteodystrophy is not a uniform bone disease. Depending upon the relative contribution of the different pathogenic factors, patients with ESRD will present different histological patterns.

Predominant Hyperparathyroid Bone Disease

Excess parathyroid hormone results in a marked increase in bone turnover. There is an abundance of osteoclasts, osteoblasts, and osteocytes (Figure 1). Disturbed osteoblastic activity results in a disorderly production of collagen, which is deposited not only toward the trabecular surface but also into the marrow cavity, causing peritrabecular and marrow fibrosis. The nonmineralized component of bone, i.e. osteoid, is increased, and the normal 3-dimensional architecture of osteoid is frequently lost. Osteoid seams no longer exhibit their usual birefringence under polarized light. Instead, a disorderly arrangement of woven osteoid and woven bone with a typical criss-cross pattern under polarized light is seen. The mineral apposition rate and number of actively mineralizing sites are increased, as documented under fluorescent light after administration of time-spaced tetracycline markers.

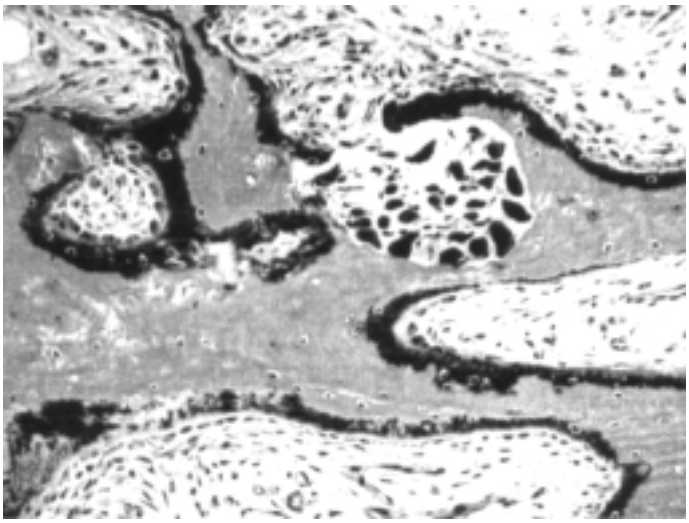

Figure 1. Predominant hyperparathyroid bone disease. High fraction of trabecular surface covered by osteoid seams; high number of osteoblasts and osteoclasts; deep resorption lacuna; marrow fibrosis; undecalcified; 3-µm-thick section of human iliac bone. Modified Masson-Goldner stain. Original magnification × 125.

Low-turnover Bone Disease

Low-turnover uremic osteodystrophy represents the other end of the spectrum of renal osteodystrophy. The histologic hallmark of this group is a profound decrease in bone turnover, i.e. a low number of active remodeling sites resulting in suppressed bone formation and bone resorption. The majority of the trabecular bone is covered by lining cells, and there are few osteoclasts and osteoblasts. Bone structure is predominantly lamellar. The extent of mineralizing surfaces is markedly reduced. Usually only a few thin single labels of tetracycline are observed. Two histologic subgroups within this type of renal osteodystrophy can be identified, depending on the sequence of events leading to a decline in the number and/or activity of the osteoblasts: low-turnover osteomalacia and adynamic bone disease.

Low-turnover osteomalacia is characterized by an accumulation of unmineralized matrix in which a diminution in mineralization precedes or is more pronounced than the inhibition of collagen deposition. Unmineralized bone represents a sizable fraction of trabecular bone volume. The increased lamellar osteoid volume is due to the presence of wide osteoid seams that cover a large portion of the trabecular surface (Figure 2). The occasional presence of woven bone buried within the trabecules indicates past high bone turnover. When osteoclasts are present, they are usually seen within trabecular bone, or at the small fraction of trabecular surface left without osteoid coating.

With adynamic uremic bone disease, the reduction in mineralization is coupled with a concomitant and parallel decrease in bone formation. It is characterized by few osteoid seams and few bone cells (Figure 3).

Mixed Uremic Osteodystrophy

Mixed uremic osteodystrophy is caused primarily by hyperparathyroidism and defective mineralization with or without increased bone

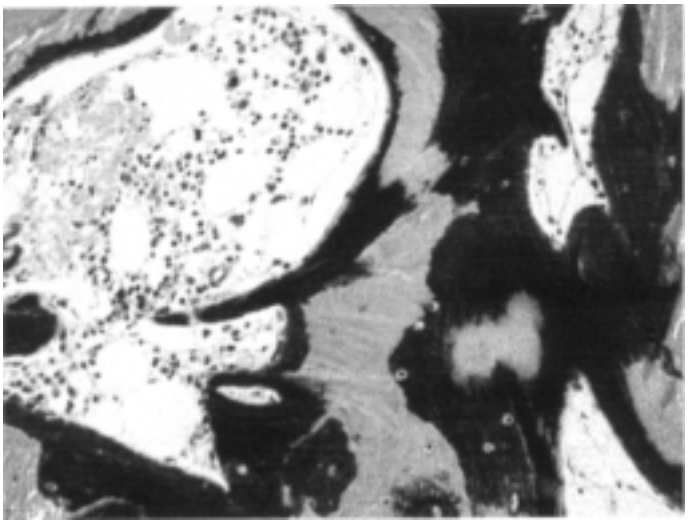

Figure 2. Low-turnover osteomalacia. Dramatically increased fraction of trabecular surface exhibiting osteoid seams; osteoid seam thickness increased; undecalcified; 3-µm-thick section of human iliac bone. Modified Masson-Goldner stain. Original magnification × 125.

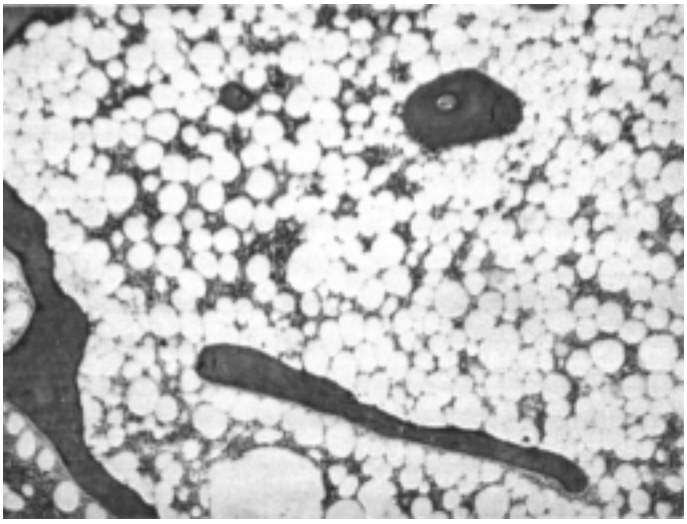

Figure 3. Adynamic bone disease. No accumulation of osteoid; absence of active resorption; undecalcified; 3 µm thick section of human iliac bone (modified Masson-Goldner stain; x 31).

formation. These features may coexist in varying degrees in different patients. Increased numbers of heterogeneous remodeling sites can be seen (Figure 4). The number of osteoclasts is usually increased. Because active foci with numerous cells, woven osteoid seams, and peritrabecular fibrosis coexist with adjacent lamellar sites with a more reduced activity, greater production of lamellar or woven osteoid causes the accumulation of osteoid with normal or increased thickness of osteoid seams. While active mineralizing surfaces increase in woven bone with higher mineralization rate and diffuse labeling, mineralization surfaces may be reduced in lamellar bone with a decreased mineral apposition rate.

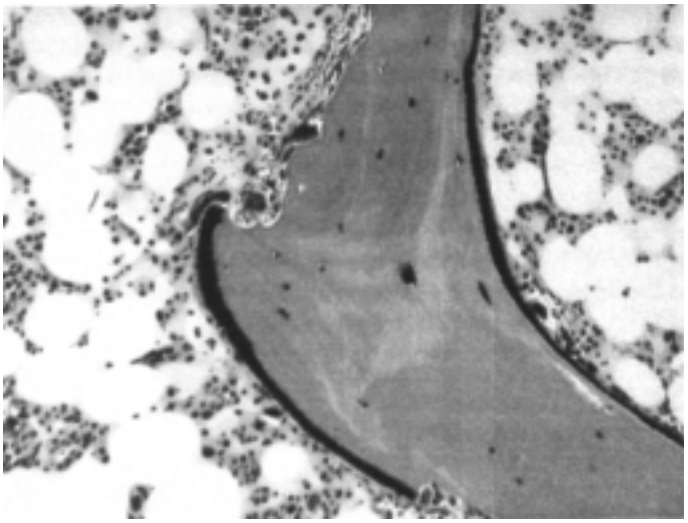

Figure 4. Mixed uremic osteodystrophy. Resorption lacunae with osteoclasts and peritrabecular fibrosis; increase in osteoid volume and surface; undecalcifed; 3-µm-thick section of human iliac bone. Modified Masson-Goldner stain. Original magnification × 200.

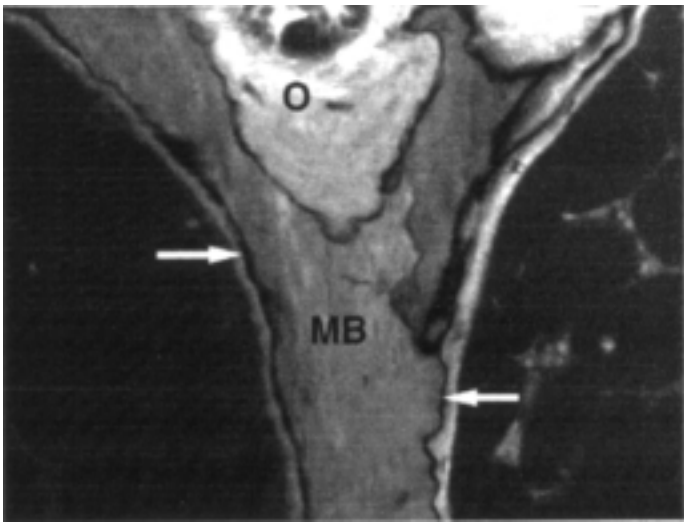

Figure 5. Aluminum deposits in bone (white arrows). Stainable bone aluminum at the osteoid (O)-mineralized bone (MB) interface, i.e. the mineralization front;. Undecalcified, 3 µm thick section of human iliac bone (aurin-tricarboxylic acid stain; × 200).

Associated Features

Bone Aluminum Accumulation

Aluminum accumulates in bone at the mineralization front (Figure 5), at the cement lines, or diffusely. The extent of stainable aluminum at the mineralization front correlates best with histologic abnormalities in mineralization. Aluminum deposition is most severe in cases of low-turnover osteomalacia. However, it can be observed in all histologic forms of renal osteodystrophy. In patients who develop increased aluminum burden, bone mineralization and bone turnover progressively decrease. These abnormalities are reversed with removal of the aluminum.

Osteoporosis and Osteosclerosis

With progressive loss of renal function, there is an increase in cancellous bone volume accompanied by a loss in cortical bone. In patients on chronic dialysis, there might be loss or gain in bone volume depending on bone balance. In case of negative bone balance, bone loss occurs in cortical and cancellous bone and is more rapid when bone turnover is high. When the bone balance is positive, osteosclerosis may be observed when osteoblasts are active in forming new bone exceeding bone resorption. When bone turnover is low, however, positive bone balance is often associated with hypercalcemia and possibly extraosseous calcifications.

β_2-Microglobulin-related Bone Disease

β_2-microglobulin (β_2-MG) amyloidosis represents osteoarthropathy and not a direct abnormality of bone remodeling in uremia. However, it is appropriate to consider it as an associated feature of ROD for 2 reasons: its clinical presentation can mimic other forms of ROD, and growing evidence suggests a direct or indirect effect of β2-microglobulin on bone metabolism.

β_2-MG is a polypeptide with a molecular weight of 11,800 daltons found on the surface of nucleated cells as part of the human leukocyte antigen (HLA) class I antigen complex [155 – 157]. Its concentration invariably increases in patients with renal failure since the kidney plays a major role in its catabolism [156, 158, 159]. Furthermore, β_2-MG production is influenced by various cytokines [160 – 162], many of which are increased in patients with ESRD [163]. The mechanism(s) that lead to the formation of β_2-MG amyloid fibrils and their predilection to be deposited in periarticular tissues are currently under study [164 – 166]. The type of HD membranes may affect β_2-MG concentrations [167]; however, β_2-MG amyloidosis is not limited to HD patients. It has been observed in continuous ambulatory peritoneal dialysis (CAPD) and CRF patients [168, 169].

In rats, Canalis et al. have identified a bone-derived growth factor as β_2-MG [170]. It is suspected that β_2-MG enhances bone growth by modulating other known growth factors such as insulin-like growth factor I [145, 171]. Similarly, β_2-MG may facilitate bone resorption by increasing the production of tumor necrosis factor or interleukin-1 [172 – 174]. Therefore, it is possible that the increased levels of β_2-MG in ESRD patients may interfere with normal bone metabolism and contribute to the spectrum of renal osteodystrophy independently from the clinical syndrome of β_2-MG amyloidosis.

Clinical Manifestations of ROD

Patients with mild to moderate renal insufficiency are rarely symptomatic. Symptoms appear in patients with advanced renal failure. However, clinical manifestations are preceded by an abnormal biochemical profile that should alert the physician and prompt steps to prevent more severe complications. When symptoms occur, they are usually insidious, subtle, nonspecific, and slowly progressive. Patients with ESRD are prone to develop a variety of symptoms related to alterations in bone and mineral metabolism.

Bone Pain, Fractures, and Skeletal Deformities

Bone pain is usually vague, ill defined, and deep-seated. It may be diffuse or localized in the lower back, hips, knees, or legs. Weight bearing and changes in position commonly aggravate it. Bone pain may progress slowly to the degree that patients are completely incapacitated. Bone pain in patients with ESRD usually does not exhibit physical signs; however, local tenderness may be apparent with pressure. Occasionally, pain can occur suddenly at one joint of the lower extremities mimicking acute arthritis or periarthritis not relieved by heat or massage. A sharp chest pain may indicate rib fracture. Spontaneous fractures or fractures after minimal trauma may also occur in vertebrae (crush fractures) and in tubular bones.

Bone pain and bone fractures can be observed in all patients with ESRD, independently of the underlying histologic bone disease, especially when osteoporosis is present. However, low-turnover osteomalacia and aluminum-related bone disease are associated with the most severe bone pain and the highest incidence of fractures and incapacity.

Skeletal deformities can be observed in children and adults. Most children with ESRD present with growth retardation and may develop bone deformities due to vitamin D deficiency (rickets) or secondary hyperparathyroidism. In rickets, there is bowing of the long bones, especially tibiae and femora, with typical genu valgum, which becomes more severe with adolescence. Long-standing secondary hyperparathyroidism in children may be responsible for slipped epiphysis due to impaired transformation of growth cartilage into regular metaphyseal spongiosa. This complication most commonly affects the hips, becomes obvious in preadolescence, and causes limping but is usually painless. When radius and ulna are involved, ulnar deviation of the hands and local swelling may occur. In adults, skeletal deformities can be observed in cases of severe osteomalacia or osteoporosis and include lumbar scoliosis, thoracic kyphosis, and recurrent rib fractures.

Myopathy

Proximal muscle weakness is fairly common in dialysis patients, particularly in those with aluminum toxicity, severe hyperparathyroidism, or osteomalacia. Its onset is usually gradual and mainly affects the lower extremities. Proximal myopathy is manifested by difficulty in rising out of a chair or climbing stairs. Patients may have a characteristic waddling gait.

Pruritus

Itching affects 40 – 90% of patients with ESRD. Pruritus can occur before institution of dialysis and can disappear after regular dialytic therapy. However, symptoms more often begin about 6 months after the start of dialysis and persist thereafter. Pruritus may be localized and mild or generalized and severe, preventing sleep and interfering with the patients normal activities.

The mechanisms underlying pruritus in ESRD patients are poorly understood. Several possible factors have been implicated (alone or in combination) such as secondary hyperparathyroidism, hypercalcemia, increased calcium-phosphorus (Ca-Pi) product, but also dry skin (xenosis), intradermic microprecipitation of divalent ions, peripheral neuropathy, allergic reactions, hypersensitivity, histamine, proliferation of skin mast cells, hypervitaminosis A, iron deficiency, and abnormal fatty acid metabolism.

Soft Tissue Calcifications, Tumoral Calcinosis, and Calciphylaxis

Asymptomatic vascular calcifications are common in patients with ESRD. Soft tissue calcifications may occur in the eyes presenting as band keratopathy in the sclerae or inducing an inflammatory response known as the "red eye syndrome" in the conjunctiva. These types of calcifications are usually associated with hyperparathyroidism or increased Ca-Pi product. Ca deposits are also found in the lungs, leading to restrictive lung disease. Deposits in the myocardium might cause arrhythmias, annular calcifications, or myocardial dysfunction. Most soft tissue calcifications are attributed to secondary hyperparathyroidism or to the increased Ca-Pi product associated with it. However, they have also been described in patients with adynamic bone disease. This could be explained by increased Ca and/or phosphate release from bone in patients with severe hyperparathyroidism and inability to maintain normal mineral accretion in patients with adynamic bone disease.

Tumoral calcinosis is a form of soft tissue calcification that usually involves the periarticular tissues. Ca deposits may grow to enormous sizes and interfere with the function of adjacent joints and organs. While this type of calcification is usually associated with high Ca-Pi product, its exact pathogenesis is poorly understood. It may also be associated with certain ill-defined intrinsic factors. Similar to soft tissue calcifications, it is observed with severe hyperparathyroidism and low-turnover bone disease.

The syndrome of calciphylaxis is characterized by vascular calcifications of the tunica media. These induce painful violaceous skin lesions that progress to ischemic necrosis. This syndrome is associated with serious complications and often death. Calciphylaxis has been associated with high serum Ca-Pi product and severe secondary hyperparathyroidism. However, it can also be seen in patients with normal or mildly elevated serum Pi or PTH levels. The pathogenesis of calciphylaxis is probably multifactorial because hyperparathyroidism, high Ca-Pi product, steroid therapy, vitamin D therapy, iron overload, aluminum toxicity, and protein C deficiency have all been implicated.

Dialysis Dementia

Clinically, dialysis dementia represents progressive neurological abnormalities that include dysarthria, dysphagia, amnesia, apraxia, mutism, myoclonic jerks, facial grimacing, seizures, and ultimately severe dementia and death. This condition is usually associated with severe aluminum accumulation.

Diagnosis

The only unequivocal tool for the exact diagnosis of renal osteodystrophy is bone biopsy for mineralized bone histology after tetracycline double labeling and aluminum staining. It determines, on the same bone sample, the precise level of bone formation, mineralization, bone resorption, bone turnover, and the extent of bone aluminum deposition, if present. The results serve as a basis for appropriate use of tailored therapeutic regimens.

In the absence of bone biopsy, the physician needs to estimate the level of bone turnover, presence of osteomalacia, and the possibility of bone aluminum toxicity. Abnormalities in serum Ca, Pi, and alkaline phosphatase levels indicate severe renal osteodystrophy but are

useless when used alone to indicate bone turnover or osteomalacia. Hypercalcemia may be observed in severe hyperparathyroidism or adynamic bone disease, especially with vitamin D therapy. Hyperphosphatemia indicates noncompliance with phosphate binders and/or severe hyperparathyroidism because of increased release of Pi from bone. High serum levels of alkaline phosphatase are usually seen in both osteomalacia and predominant hyperparathyroidism.

Skeletal X-ray abnormalities are seen when the disease is advanced [175]. They include erosive cortical defects in the skull ("pepper pot skull"), acroosteolysis of the clavicula, and erosion of the terminal finger phalanges. A rugger jersey appearance of the spine, a ground glass appearance of the skull, ribs, pelvis, and metaphysis of tubular bones reflect advanced cancellous changes. In severe hyperparathyroid bone disease, pseudocysts or brown tumors may be observed. However, signs of increased bone resorption may be seen on x-rays reflecting past resorbing activity, which may have been succeeded by accumulation of osteoid. Since osteoid is radiolucent, the superimposed osteomalacia will be missed by X-ray examination. Looser zones that are straight bands of radiolucency abutting onto the cortex and running perpendicular to the long axis of bone are of relatively low sensitivity and low specificity for the diagnosis of osteomalacia.

Serum PTH levels are better indicators of bone turnover, especially when measured with the immunoradiometric assay that detects only the intact hormone. However, a careful assessment of the predictive value of serum PTH levels for bone turnover shows that all patients with serum PTH levels within or below the normal range (< 65 pg/mL) have low bone turnover, and that values of serum PTH levels > 450 pg/mL are 100% and 95.5% specific for high bone turnover in patients on HD and PD, respectively [176]. For the majority of dialyzed patients, i.e. those with serum PTH levels between 65 and 450 pg/mL, bone turnover cannot be predicted accurately [176]. In addition to serum PTH values, certain risk factors for low bone turnover have been isolated such as PD, diabetes (DM), advanced age, high Ca content in dialysate, high doses of phosphate binders, aggressive vitamin D therapy, or previous parathyroidectomy. However, in individual patients, discrepancies between risk factors, PTH levels, and bone turnover are frequent, and this calls for bone biopsy.

Aluminum accumulation may be seen at any level of bone turnover or serum PTH levels. Although correlations exist between random serum aluminum levels and the extent of stainable aluminum in bone, no threshold value allows a clear-cut distinction between patients with and patients without aluminum-related bone disease. Deferoxamine (DFO) infusion test is advocated to improve the sensitivity of random serum aluminum levels. An increase in serum aluminum levels > 200 µg/L 48 hours after a standardized infusion constitutes a positive result. This test does improve the sensitivity of predicting aluminum-related bone disease, but specificity is greatly reduced. Both a positive DFO test and a PTH level < 200 pg/mL will make the diagnosis of aluminum-related bone disease with almost absolute certainty. However, the sensitivity is again greatly reduced and many patients will have false negative results.

Management of Dialysis Patients with ROD

Therapeutic intervention should begin before the patient develops far-advanced bone disease, that is, not later than at the time of

institution of dialysis. Secondary hyperparathyroidism can be prevented by avoiding deviations of serum Pi and Ca levels from normal. However, one cannot be dogmatic in the management of patients with ROD, and therapeutic approaches must be tailored to meet each patients individual needs.

Control of Serum Phosphorus

Hyperphosphatemia plays a major role in the induction and maintenance of secondary hyperparathyroidism. It also contributes significantly to the development of soft tissue calcifications. Therefore, controlling serum Pi in dialysis patients is of great importance and probably constitutes the greatest challenge in the management of ROD.

Role of Dialysis

Due to the compartmentalization and slow efflux of Pi from intracellular space, all dialytic methods are inefficient in Pi removal. It is estimated that, on the average, only 3 g of Pi/week can be removed by dialysis. Therefore, in patients with ESRD one must rely on strict dietary Pi restriction and the use of phosphate binders in order to achieve appropriate phosphate control. However, it has been shown recently that nocturnal dialysis 6 times a week was efficient in controlling Pi levels and prompted a reduction in intake of phosphate binders [177]

Dietary Phosphorus Restriction

Phosphate is present in most protein-containing food products. Therefore, severe Pi restriction cannot be implemented if adequate protein intake is to be maintained. With the current recommendations of dietary protein intake in dialysis patients of 1 g/kg/day [178], it is estimated that patients will receive a minimum of 1 g Pi/day. Therefore, phosphate binders have to be used frequently in order to prevent Pi retention in anuric patients.

Phosphate Binders

Phosphate binders are most effective when given with meals and in proportion to the size of the meal [179]. Patients with persistent hyperphosphatemia should have detailed dietary counseling to insure compliance with the diet and prescription of phosphate binders.

Ca salts are currently the most widely used phosphate binders. Calcium acetate appears to be more efficient in binding Pi than calcium bicarbonate [180, 181]. Therefore, lower doses of elemental Ca can be used with calcium acetate to achieve a similar degree of Pi control [182, 183]. However, in short-term studies, these findings did not translate to fewer incidences of hypercalcemia in patients treated with calcium acetate [182, 183]. Calcium citrate bears the risk of increasing aluminum absorption [184] and thus should be avoided.

Aluminum-containing phosphate binders are now rarely used by most nephrologists. Studies indicate that the aluminum in these products is absorbed and can accumulate in dialysis patients [185 – 187]. However, aluminum-containing phosphate binders may still be used, temporarily and rarely, only in patients with severe and uncontrollable hyperphosphatemia since in these patients high doses of Ca salts may precipitate soft tissue calcifications. Once Pi levels are reduced, aluminum products should be gradually replaced by Ca salts.

In some patients, high doses of Ca salts may lead to hypercalcemia without optimal Pi control. In these instances, one must again ascertain dietary compliance and that patients are taking the phosphate binders with meals. Lowering dialysate Ca concentration helps control hypercalcemia and allows the use of

higher doses of Ca salts [188 – 190]. However, one must be sure that patients are compliant with their Ca prescriptions since low calcium dialysate without adequate Ca intake may lead to negative Ca balance [179, 191]. If this strategy fails to control hypercalcemia and correct hyperphosphatemia, judicious use of low doses of aluminum-containing phosphate binders with careful monitoring of serum aluminum might be justified. However, we feel that the continuous use of even low doses of aluminum products will invariably lead to an increase in plasma aluminum levels and result in aluminum accumulation. Some investigators suggest the use of magnesium-containing phosphate binders in conjunction with low dialysate magnesium and careful monitoring of serum magnesium levels [192, 193]. Although in one study, patients showed no adverse effect of magnesium-containing products on bone [194], magnesium is a known inhibitor of bone mineralization. Therefore, long-term effects of magnesium-containing phosphate binders on bone microstructure need further study before their routine use in dialysis patients can be recommended.

There are currently efforts to develop non-calcium and nonaluminum-containing phosphate binders. RenaGel has been recently approved by the Food and Drug Administration (FDA). Long-term effects on control of phosphate and bone histology, however, are not yet available.

In some patients, persistent hyperphosphatemia could be the result of severe hyperparathyroidism with enhanced bone resorption leading to Pi mobilization from bone. These patients need careful control of the underlying secondary hyperparathyroidism and may require parathyroidectomy.

In treating patients with hyperphosphatemia, it is important to avoid hypophosphatemia. Pi serum levels should be maintained at 4.5 – 5.5 mg/dL. The cause of hypophosphatemia in dialysis patients, when present, should be investigated and treated appropriately.

Maintenance of Serum Calcium

Intestinal Ca absorption is reduced in patients with advanced renal failure [195]. Ca supplementation in these patients can restore positive Ca balance and alleviate secondary hyperparathyroidism [118]. Thus, Ca salts in dialysis patients have dual functions: to bind Pi and to provide Ca supplementation. When Ca supplementation is needed, Ca salts should be given between meals to enhance its absorption. Serum Ca levels should be maintained in the mid to upper range of normal to ensure parathyroid gland suppression. The use of high doses of Ca salts in patients with advanced renal failure can lead to hypercalcemia since these patients are unable to compensate for high Ca administration by increasing urinary Ca excretion. In dialysis patients, serum Ca levels can be influenced by manipulating dialysate Ca concentration. This approach may facilitate the use of Ca salts as phosphate binders. However, if the balance between Ca removal during dialysis and oral administration of Ca salts is poorly maintained, the patient risks either transient increases in parathyroid gland activity or extraosseous calcifications [196].

If hypercalcemia persists despite the reduction of oral Ca intake, one must rule out the presence of severe hyperparathyroidism (high bone turnover), aluminum bone accumulation or adynamic bone disease (low bone turnover). It is also important to rule out causes other than the underlying form of ROD such as malignancy, paraproteinemia, immobilization, granulomatous diseases, and other known etiologies of hypercalcemia.

Vitamin D Therapy in Dialysis Patients

Calcitriol

The use of calcitriol to control secondary hyperparathyroidism in dialysis patients is an established practice. However, its use is not without complications and limitations. There are also numerous questions regarding to the optimal time and route of administration.

Many studies have described a beneficial effect of daily oral $1,25(OH)_2D$ on biochemical, radiological and histological signs of hyperparathyroid bone disease [197, 198]. However, hypercalcemia is a rather common side effect of this therapy, requiring temporary cessation of the drug. Slatopolsky et al. found that intravenous (IV) administration of $1,25(OH)_2D$ suppresses PTH levels with decreased incidence of hypercalcemia [199]. Oral intermittent therapy (2 – 3 times/week) has also been shown to be effective in controlling hyperparathyroidism [200 – 204] indicating that intermittent high peak levels of calcitriol in addition to the route of administration are important for PTH suppression.

We observed that the incidence of hypercalcemia was higher in patients receiving PO than IV pulse therapy [205]. On the other hand, hyperphosphatemia and increased Ca-Pi product were the major limiting factors in the efficacy of IV therapy [205]. To minimize these side effects, some investigators advocate the use of low-dose IV calcitriol as a safe and effective therapy in controlling secondary hyperparathyroidism in HD patients [206, 207]. In our experience the therapeutic window of pulse calcitriol therapy is limited, and high doses are frequently needed in order to achieve significant reduction in PTH serum levels [205]. In CAPD patients, both subcutaneous (SC) and intraperitoneal (IP) administration of calcitriol have been described as effective in controlling hyperparathyroidism [208, 209]. However, their advantage over oral administration is not established [210].

The optimal serum PTH levels in dialysis patients have not yet been established. Customarily, nephrologists try to maintain intact PTH levels at 1.5 – 2 times the upper range of normal. It was recently suggested that uremic patients require 2.5 × normal intact PTH to maintain normal bone turnover [211]. We observed that serum levels of intact PTH between 65 – 450 pg/mL are a poor predictor of the underlying bone turnover. Only with levels > 450 pg/mL can one predict with certainty the presence of high bone turnover [212]. Therefore, serum PTH levels should not be aggressively suppressed with PO or IV calcitriol unless evidence of high bone turnover is substantiated by bone biopsies. The role of bone markers, i.e. osteocalcin, alkaline phosphatase, and hydroxyproline in guiding calcitriol therapy needs further study. Similarly, further studies are needed to assess the efficacy and safety of long-term IV vs. pulse PO calcitriol therapy. Currently, there are no controlled studies to evaluate who should get daily or pulse PO therapy for supplementation of a missing hormone vs. suppression of parathyroid gland overactivation.

Other Vitamin D Metabolites

The optimum vitamin D metabolite for maintenance therapy should maintain the cellular differentiating effect of vitamin D with only mild antiproliferative effects. In addition, this metabolite should have a limited effect on intestinal Ca absorption and serum Ca. This metabolite would obtain a balance between the satisfactory suppression of parathyroid gland and adequate bone turnover without hypercalcemia.

Several endogenous and synthetic vitamin D metabolites are available and hold promise for the treatment of secondary hyperparathyroidism [213]. 1α-hydroxyvitamin D (alfa-

calcidol) has been shown to be effective in suppressing PTH in dialysis patients [214, 215] but probably has no advantage over calcitriol. The effect of 24,25$(OH)_2$D alone on secondary hyperparathyroidism is controversial [216]. However, a recent report advocates its use in combination with calcitriol [217]. This combination may effectively reduce bone resorption without affecting bone formation. 22-oxa-1,25$(OH)_2$D (OCT) has gained recent attention as a potent suppressor of PTH secretion with relatively less effect on intestinal Ca absorption [218, 219]. In nephrectomized dogs, OCT was efficient in preventing the increase in serum PTH levels. However, some episodes of hypercalcemia were observed [220]. Interestingly, however, OCT did not suppress bone turnover and thus appears unlikely to induce adynamic bone disease [220]. 19-Nor-1-alpha-25-dihydroxyvitamin D_2 (Zemplar) has been recently introduced as a less hypercalcemic vitamin D analog for control of secondary hyperparathyroidism [221]. However, its effects on bone are not known at this time.

Parathyroidectomy

Surgical parathyroidectomy is currently reserved for patients with overt hyperparathyroidism (symptomatic or progressive) who do not respond to vitamin D therapy or who develop side effects from such therapy. Indications for parathyroidectomy include:

- Patients with persistent hypercalcemia despite adjustments in dialysate Ca concentration. These patients must demonstrate histological evidence of severe hyperparathyroidism without aluminum accumulation prior to being subjected to surgical parathyroidectomy.
- Patients with persistent hyperphosphatemia and high Ca-Pi product despite aggressive dietary counseling and compliance with prescriptions. Prior to parathyroidectomy, these patients must also have histological evidence of severe accelerated bone resorption that would explain the presence of persistent hyperphosphatemia.
- Patients with progressive and symptomatic soft tissue calcifications, including the syndrome of calciphylaxis. Again, these patients must have biochemical and histological evidence of hyperparathyroidism with high bone turnover at the time of parathyroidectomy.
- Patients with severe progressive and symptomatic hyperparathyroidism when rapid reduction in PTH is required and vitamin D pulse therapy has failed. These patients usually have significant increase in their parathyroid gland size.
- Patients with refractory pruritus. Prior to parathyroidectomy, these patients must have evidence of severe hyperparathyroidism and have failed all other remedies for itching.

There are 3 surgical approaches to parathyroidectomy: subtotal parathyroidectomy, total parathyroidectomy with parathyroid autotransplantation, and total parathyroidectomy. Each approach has its own merits and complications [222]. Subtotal parathyroidectomy risks the possibility of inadequate reduction in parathyroid gland mass or the recurrence of hyperparathyroidism in the remaining tissue. Both of these possibilities require re-exploration of the neck, which can be technically difficult due to the formation of scar tissue. Total parathyroidectomy with parathyroid autotransplantation in the forearm allows an easy access to the residual parathyroid tissue, should this be necessary. However, there have been reports of migration of the transplanted gland cells into the venous circu-

lation and the muscles of the forearm [223 – 225]. Furthermore, the aggressive use of vitamin D in the prevention or treatment of hypocalcemia post-parathyroidectomy may interfere with the successful autotransplantation of the parathyroid tissue. This may lead to severe postoperative hypoparathyroidism. Finally, total parathyroidectomy has been advocated to reduce the risk of recurrence [226]. Surprisingly, postsurgical symptoms of hypoparathyroidism were mild or absent. However, further studies are needed to evaluate this procedure carefully.

A recent randomized study evaluating subtotal parathyroidectomy and total parathyroidectomy with autotransplantation showed that the latter was superior in regard to normalization of serum Ca and alkaline phosphatase, improvements in clinical and radiographical abnormalities, and recurrence rate of hyperparathyroidism [227]. However, another study revealed a very high recurrence rate after total parathyroidectomy with autotransplantation [228]. It is clear that prospective randomized trials comparing all these surgical procedures are needed before recognizing the best approach.

Recently, percutaneous ethanol injection under ultrasound guidance was described as an alternative to surgical parathyroidectomy [229 – 232]. Patients may require multiple injections at weekly intervals for better results. The main complication of this procedure is transient [230] or permanent [233] paralysis of the recurrent laryngeal nerve. It is also possible that fibrosis of the surrounding tissues induced by alcohol may render subsequent surgical parathyroidectomy technically difficult. Therefore, current knowledge of this innovative procedure indicates that this treatment should be reserved only for patients unfit for surgery.

Patients undergoing parathyroidectomy require careful follow-up and meticulous management. Postoperative hypocalcemia should be anticipated and treated with PO and IV calcium. The use of calcitriol may minimize the need for large doses of Ca salts; however, it may interfere with the successful uptake of the transplanted gland. A reasonable approach would be the use of IV calcitriol administered at the end of each dialysis treatment for 2 – 3 treatments prior to parathyroidectomy [222] followed by the lowest dose of PO calcitriol needed. Preferably, the PO use of calcitriol post-parathyroidectomy with autotransplant should be delayed for a few days. Another potential complication of parathyroidectomy is the propensity of patients to accumulate aluminum [234 – 237]. Therefore, we strongly suggest that patients undergo a bone biopsy prior to parathyroidectomy to rule out with certainty the presence of aluminum accumulation in bone.

Aluminum Removal

Any therapeutic maneuver that lowers plasma aluminum levels and creates a concentration gradient across the bone-extracellular fluid membrane will be able to move aluminum from bone to blood. Aluminum is 80% protein bound; therefore, only 20% of total aluminum is ultrafilterable. The elimination of aluminum from bone through normal turnover and by completely withdrawing aluminum sources is very slow and may take years. However, aluminum removal is greatly enhanced by the use of a chelator agent. A highly specific and completely safe chelator of aluminum does not exist. Deferoxamine (DFO) is presently the best chelator of aluminum. DFO increases the complex-bound fraction of aluminum and facilitates its removal through dialysis. DFO is relatively safe, but rare ocular complications such as cataracts, altered color vision, night blindness, or scotoma have been

reported [238]. Episodes of hypotension due to a histamine-mediated vasodilatory effect of the drug can occur during DFO therapy. Hypotension can be precipitated by rapid infusion (> 15 mg/kg/hour) and the use of low-calcium dialysate. It is usually easily reversible; however, in some cases angina has been reported. Nausea, vomiting, and neuromuscular excitability are usually transient. The association between DFO therapy and infections has been the subject of controversy. DFO is thought to act as siderophore and therefore may promote bacterial and fungal infections [239, 240]. Although numerous case reports of bacteremia and mucormycosis occurring with DFO therapy have been published, a large survey did not confirm that DFO increases the risk of bacteremia in dialysis patients [241]. The possible relationship between DFO therapy and mucormycosis, though rare, represents a very serious complications that deserves careful further investigation. Therefore, unequivocal documentation of aluminum overload is required before long-term DFO therapy is begun.

After DFO infusion, increases in serum aluminum levels are observed indicating the translocation of aluminum from bone and other organs into the blood. Peak levels decrease with time and reach baseline values after 3 – 12 months depending on the extent of initial aluminum overload [242]). Therapy should be discontinued when no increases in serum aluminum levels are seen 48 hours after infusion, and particularly when zero dialysance is observed. Failure to withhold therapy at this stage may lead to the chelation of other trace metals [243] and subject patients to the unnecessary risks of DFO side effects.

The optimal dose of DFO is not clearly established. Currently, based on the non-linear dose-chelation curves, most nephrologists are using lower doses than before. An appropriate dose range appears to be 5 – 20 mg/kg, 1 – 3 times/week infused slowly over 2 hours. Infusion of DFO at the end of dialysis is potentially more efficient since it allows the chelator to act longer. However, this bears the risk of inducing long-standing high serum levels of aluminum that could be redistributed to the brain causing acute encephalopathy. In CAPD patients, intramuscular (IM) or overnight IP DFO therapy has been advocated as an effective method [244, 245]. However, our experience indicates that IV administration during the last 2 hours of HD is preferable in patients with severe aluminum intoxication (> 90% of trabecular surface). The added expense and logistical problems of using special cartridges with microencapsulated carbon [246, 247] or DFO coating limit their application to severe aluminum toxicity when time is of the essence.

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Comorbid Conditions and Special Problems in Dialysis Patients

Eric W. Young

Renal failure seldom exists as an isolated clinical entity. Rather, renal patients usually manifest other non-renal medical conditions. These comorbid conditions greatly modify clinical outcomes and medical resource utilization, as do major demographic characteristics such as age, race, sex, and socioeconomic status. The distribution of comorbid conditions and demographic characteristics among patients describes the case mix of a population (e.g. all dialysis patients, all end-stage renal disease (ESRD) patients, all patients in a dialysis unit).

Comorbidity generally refers to the additional (non-renal) illnesses present in a patient or population at a given time, such as start of ESRD or start of a year. Comorbidity can obviously change over time. In the specific context of ESRD, comorbid conditions may be present when renal replacement therapy (RRT) is initiated. Such baseline comorbid conditions may have caused or contributed to the development of kidney failure. Diabetes mellitus (DM) and systemic vasculitis illustrate comorbid conditions of this type. Alternatively, comorbid conditions may develop after the onset of kidney disease, perhaps as a direct or indirect consequence of renal failure and its treatment. Renal osteodystrophy and anemia exemplify this pattern of comorbidity. The relationship between renal disease and a comorbid condition may be bi-directional. For example, conditions such as hypertension may both contribute to and result from renal failure. All comorbid conditions can potentially influence mortality, morbidity, quality of life, and utilization of medical resources. This chapter considers some of the most common comorbid conditions associated with ESRD, without regard for causality.

Comorbid conditions are important for several reasons. Comorbidity should be considered for epidemiologic research and quality improvement activities. Important clinical outcomes, such as mortality, hospitalization, and quality of life, are greatly influenced by patient comorbidity in addition to demographic characteristics and treatment practices. Thus, comorbidity adjustment is potentially needed for proper assessment of outcomes and clinical performance. Comorbidity is also a major determinant of the resources required to care for patients with ESRD. On average, comorbid illnesses require additional medical services such as hospitalization, procedures, and specialty care. Patient comorbidity can be important for understanding the causes and consequences of renal failure. Finally, the provision of medical care to ESRD patients largely entails the treatment of comorbid conditions. Modern dialysis and transplantation techniques can usually control the direct clinical consequences of renal failure such as fluid overload, hyperkalemia, and the uremic syndrome. Most of the major medical problems faced by ESRD patients

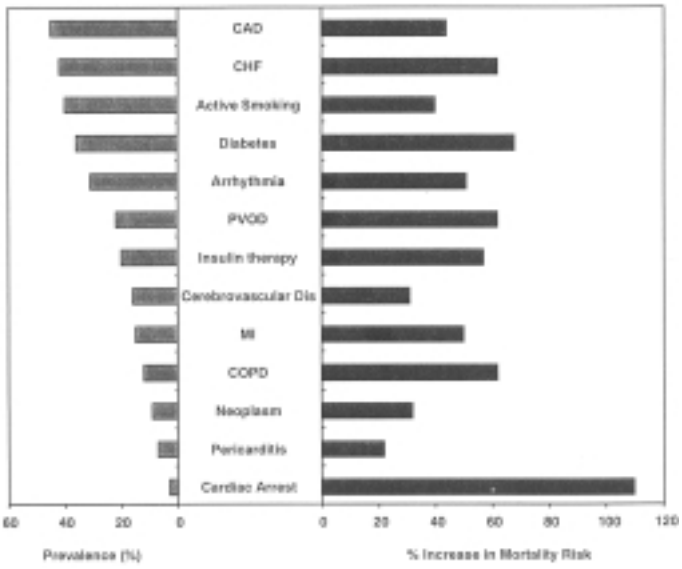

Figure 1. Prevalence (left panel) and mortality risk (right panel) associated with selected comorbid conditions in ESRD patients. Data taken from USRDS 1995 Annual Data Report.

arise from comorbid diseases rather than renal failure. Consequently, most hospitalizations and deaths among ESRD patients are attributable to comorbid conditions. A similar accounting of comorbidity from other countries might reveal interesting contrasts in the nature and consequences of comorbidity among different groups of ESRD patients.

Among a defined group of patients, the proportion with a given comorbid condition is expressed as the prevalence. The rate at which a comorbid condition appears among individuals previously lacking the condition is expressed as incidence. For renal patients, considerably more is known about the prevalence than the incidence of most comorbid conditions. Although the severity of a given comorbid condition can vary greatly in clinical terms, uniform and validated severity measures are poorly developed at this time. The degree to which an outcome, such as mortality, is associated with a baseline comorbid condition is measured by the relative risk. The deviation of relative risk above 1.0 indicates the excess mortality associated with the attribute as compared to the group of individuals lacking the attribute. For example, a relative risk of 1.2 indicates a 20% increase in mortality. If the baseline death rate is 25%, then a relative risk of 1.2 translates into an absolute risk of 30%.

Comorbid Conditions Associated with ESRD

Figure 1 shows the prevalence of several important comorbid conditions associated with ESRD from a randomly selected, nationally representative group of hemodialysis (HD) patients in the U.S. [1]. The list, while not exhaustive, is useful for prioritizing the many specific comorbid conditions that are seen in ESRD patients. The figure also illustrates the relative mortality risk associated with each comorbid factor, as derived from a multivariate regression model of survival. Subject to several assumptions, the model estimates the independent effect of each comorbid condition on mortality under the addi-

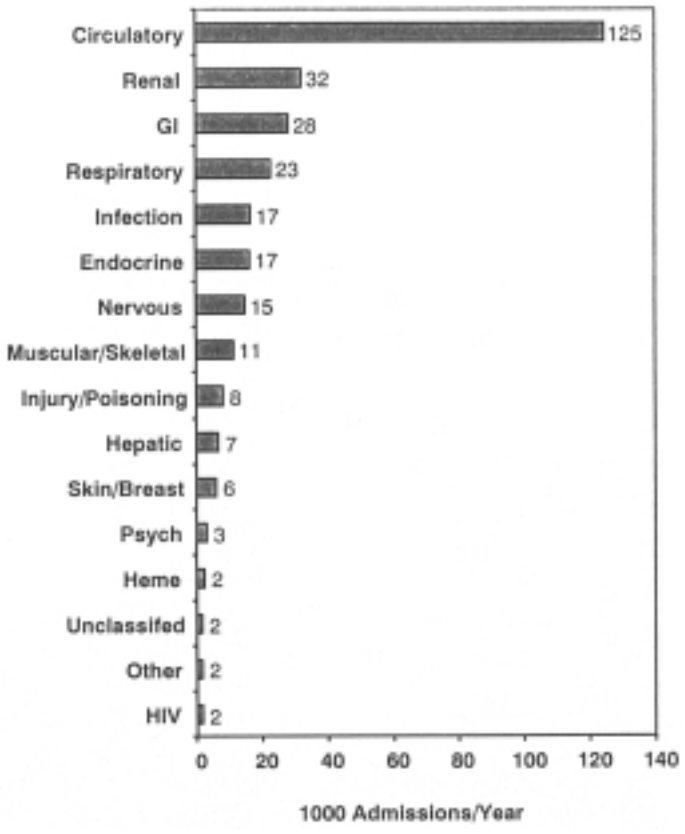

Figure 2. Hospital admission rates for ESRD patients by selected disease categories. Data taken from USRDS 1997 Annual Data Report.

tional assumption that all other modeled characteristics (demographic and comorbid factors) are held constant. For example, coronary artery disease (CAD) was present in 45% of the patient sample. As a group, the patients with CAD had a 44% higher chance of death compared to patients lacking a baseline diagnosis of CAD. The prevalence and risk of any given comorbid condition tends to vary among studies, reflecting differences in case-mix. The comorbidities described in Figure 1 are broadly applicable to all HD patients in the U.S. The impact of comorbid conditions is further illustrated by Figure 2, which shows the major reasons for hospitalization, and by Figure 3, which shows the most common causes of death among U.S. dialysis patients [2]. These figures highlight the importance of comorbidity from a clinical outcomes viewpoint.

The prevalence of most comorbid conditions has increased over time, even after adjustment for differences in race, sex, and, especially, age [3, 4]. Increasing comorbidity among new ESRD patients could be explained by liberalization over time of the implicit criteria for referral and acceptance of patients for RRT. Another explanation for this trend is that survival has been increasing for patients at risk for developing ESRD but prior to the actual onset of ESRD. Improved patient survival in the pre-ESRD phase is plausibly attributable to improvements in the treatment of comorbid conditions, primarily cardiovascular diseases. The extended survival of patients with atherosclerotic CAD and other ill-

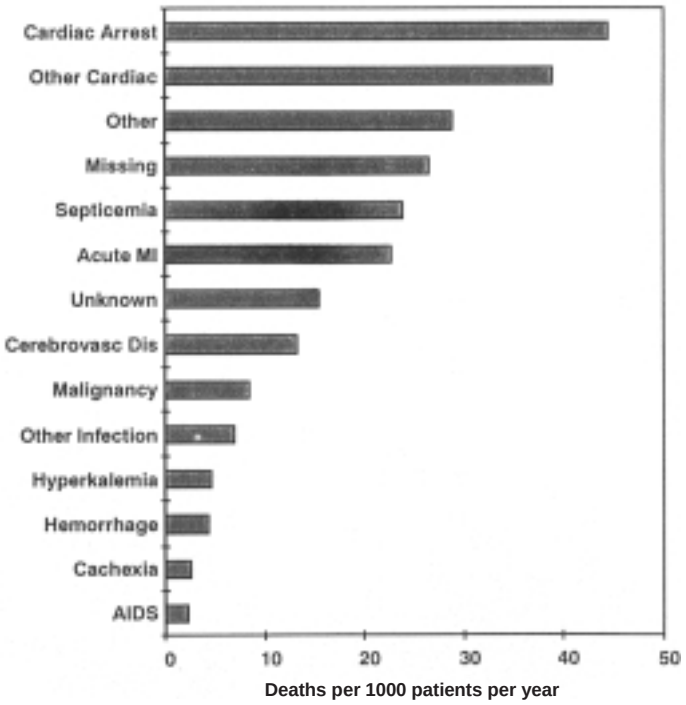

Figure 3. Distribution of deaths by cause for dialysis patients. Data taken from USRDS 1997 Annual Data Report..

nesses allows more time for the development of ESRD. This reduction in competing risk factors may partially explain the steady growth in new ESRD cases over the past 10 – 20 years [1].

The topic of comorbid conditions associated with renal failure encompasses nearly all of medicine. This chapter presents a brief discussion of selected comorbid conditions that are particular common or noteworthy. The discussion emphasizes prevalence, risk associations, and topical or evolving clinical information.

Diabetes Mellitus (DM)

DM is the single most common attributed cause of ESRD and a major comorbid condition. In a recent large national study of ESRD patients, DM was reported as a comorbid factor in 36% of patients whereas it was the attributed cause of ESRD in 27% of patients (Figure 1) [1]. Thus, DM is present or develops in a substantial number of patients in whom renal failure is caused by another disease. This point notwithstanding, the designation of DM as a comorbid condition is based on attributed cause of ESRD in many studies.

DM is clearly associated with increased mortality (Figure 1) and is an important adjustment factor (along with age, race, and other major causes of ESRD) for calculating the standardized mortality rate (SMR) for a dialysis unit [5]. DM disposes to accelerated atherosclerosis, a major factor in diseases of both large and small blood vessels. DM is also associated with excess formation of advanced glycosylation products, glycoproteins than bind to tissues in a non-enzymatic irreversible

fashion and disrupt cell functions. DM also disposes to infections, due in part to vascular disease and impairment of integumentary barriers and other host defense mechanisms. Retinopathy, peripheral vascular disease, and peripheral neuropathy often precede ESRD in diabetic patients. In general, the very fact of ESRD underscores the impact and severity of the disease in a diabetic individual.

Treatment considerations for patients with DM are discussed elsewhere. It is important to realize that insulin requirements may decrease with progressive kidney failure and ESRD due to loss of normal renal insulin elimination. The fall in insulin requirements in no way signifies any improvement in the underlying disease. Also, good glucose control should remain a goal even after initiation of dialysis. Although the goal of preventing renal injury may seem moot, it remains important to protect against further injury at other sites such as the eyes. Glycemic control may also be important for preserving residual renal function for as long as possible.

Hypertension

The prevalence of hypertension exceeds 70% among ESRD patients [6]. Hypertension often precedes the onset of ESRD. In the absence of other known renal diseases, renal failure is often attributed to hypertensive nephrosclerosis although it is realized that a variety of other etiologically important but otherwise nondescript diseases could be misdiagnosed as hypertension [7, 8]. Furthermore, renal failure usually stimulates blood pressure elevation in previously normotensive individuals and exacerbates hypertension in patients with pre-existing high blood pressure.

The etiology and pathogenesis of essential hypertension remains incompletely understood and classified at this time despite intensive investigation of this common condition. However, hypertension in renal patients is thought to be mediated by volume expansion in as many as 50 – 90% of cases [9, 10]. Hypertension is specifically associated with markers of long-term volume expansion, such as the diameter of the inferior vena cava and total body water [11, 12]. In accordance with this observation, aggressive ultrafiltration (UF) programs based on long (e.g. 8 hours) dialysis sessions have been associated with a decreased prevalence and severity of hypertension [13, 14]. Despite the apparent benefits of aggressive UF associated with long dialysis sessions, it is usually not practical to perform 8-hour treatments on a routine basis and methods have not been fully developed for achieving excellent UF and blood pressure control in large numbers of ESRD patients. Short, daily, home HD has been advocated as a practical method of lowering dry weight, blood pressure, and mortality. However, enthusiasm for such approached must be tempered by the studies that have found only small or negligible blood pressure elevations associated with intra-dialytic fluid gains and short-term volume loading [15, 16]. Discrepancies among current studies regarding the relationship between volume status and blood pressure may be explained by varying sensitivity of the techniques used to measure volume.

Nonetheless, the current body of evidence does not uniformly support the conventional assumption that hypertension is directly associated with adverse clinical outcomes in ESRD patients. In non-ESRD patients, blood pressure is clearly associated with increased cardiovascular morbidity and mortality. Furthermore, multiple randomized controlled trials have shown benefit from lowering blood pressure. In contrast, while some studies show

that increased blood pressure is associated with higher mortality in the ESRD population [4, 17], a surprising number of studies (some involving large numbers of patients) have not found this expected relationship [18 – 20]. While low blood pressure could plausibly be associated with high mortality due to cardiac dysfunction or coronary ischemia, it is difficult to explain the lack of association between high blood pressure and mortality. The expected relationship may be obscured by the frequent use of antihypertensive drugs in ESRD patients or by the variability in blood pressure throughout the interdialytic period but the issue requires further study.

There has been growing interest in the use of ambulatory blood pressure monitoring (ABPM) for ESRD patients. This technique is especially attractive for HD patients who experience potentially large fluctuations in blood pressure between dialysis treatments. In a recent study, the prevalence of hypertension was over 70% by ABPM compared to 25% using conventional measurements [21]. Furthermore, ABPM results were strongly correlated with the echocardiographic presence of left ventricular hypertrophy. ABPM has generally revealed a loss of the normal diurnal blood pressure pattern in patients treated with both HD [21] and peritoneal dialysis (PD) [22]. The use of ABPM may clarify the relationship between blood pressure and clinical outcomes. However, until ABPM measurement are convincingly associated with outcomes and clinical management decisions, the technique will probably be used primarily as a research tool.

Despite efforts to maximize UF, hypertension is still very prevalent in most dialysis units. Furthermore, despite the confusion about the nature of the association between blood pressure and cardiovascular outcomes in ESRD patients and the lack of controlled studies supporting the efficacy of treating ESRD patients, most experts believe that hypertension should be treated in this group of patients. At this time, pharmacologic approaches are recommended for patients whose blood pressure cannot be controlled through dialytic UF. The overwhelming body of epidemiologic and clinical trial evidence in non-ESRD patients supports this position until more definitive information emerges for ESRD patients. However, it is important to recognize that antihypertensive medications can be surprisingly ineffective in fluid-overloaded patients, whether due to inadequate dialysis or dietary non-compliance. There is very little information in ESRD patients on which to base the selection of antihypertensive medications. Beta antagonists are attractive because they have been shown to improve survival in patients with coronary artery disease, a very common comorbidity in the ESRD population. It has been argued that beta antagonists have been underutilized because of exaggerated concerns that they mask the symptoms of insulin reactions in diabetic patients [23]. Angiotensin converting enzyme (ACE) inhibitors have been claimed to decrease inter-dialytic weight gain through suppression of the central thirst mechanism [24] but this compelling finding has not been replicated [25]. However, this class of drug provides a survival advantage in non-ESRD patients with DM as well as congestive heart failure (CHF) [26]. Calcium channel blockers have enjoyed popularity because they are well tolerated but they have not undergone long-term studies and have been linked to increased coronary events [26, 27]. Blood pressure in ESRD patients is also modified by a wide variety of other dietary and treatment-related factors including salt intake, calcium intake, phosphate balance, erythropoietin administration, and red cell mass [28].

Coronary Artery Disease (CAD)

Atherosclerotic CAD is one of the most common and important comorbid conditions in ESRD patients. For classification purposes, CAD includes the current or historical presence of angina, myocardial infarction (MI), abnormal coronary angiogram, or coronary bypass surgery or angioplasty. Approximately 30 – 45% of new ESRD patients carry a diagnosis of some form of CAD, depending on the specific definition and series [1, 29]. As in the non-renal population, virtually all CAD is caused by atherosclerosis, which is associated with well known risk factors including hypertension, hyperlipidemia, smoking, and family history. These risk factors can also cause or contribute to the development of renal failure. Thus, ESRD and CAD are associated on the basis of underlying risk factors. In addition, renal disease has been hypothesized to accelerate the development and progression of atherosclerosis, leading to excess CAD in the ESRD population [30, 31]. Among ESRD patients, the presence of CAD has been associated with an increased mortality risk in some [1] but not all studies [29]. However, CAD, manifest as acute MI and cardiac arrest, is the single most common cause of death among ESRD patients, accounting for > 30% of deaths [2]. The mortality risk of CAD is augmented in patients with concomitant CHF [29].

The clinical presentation of CAD in ESRD patients is usually similar to non-renal patients. However, atypical presentations may occur, particularly in diabetic patients who are prone to silent ischemia and painless myocardial infarctions [32]. The sensitivity of non-invasive stress testing appears to be lower in renal patients than in non-renal patients [33]. Dobutamine stress echocardiography may be more sensitive than other techniques for inducing stress and detecting ischemia [34]. All else being equal, the clinical threshold for performing coronary angiography should be lower for ESRD patients than for non-renal patients.

Coronary ischemia can be treated either medically or through revascularization procedures. The usual factors should dictate the decision. Medical therapy with nitrates, beta antagonists, calcium antagonists and correction of anemia should be fully explored. The evidence that beta antagonists lower mortality from coronary disease is especially strong and it has been suggested that these agents are underutilized in ESRD patients [23]. In contrast, calcium antagonists have been less well studied altogether and, although attractive drugs in terms of patient tolerability, may be used more often than justified by current evidence. In some centers, there is a reluctance to perform revascularization procedures in ESRD patients because of their poor average survival and perceived high risk status. An individualized approach that considers the patients overall status should be used. The available evidence indicates that ESRD patients accrue similar benefits from revascularization procedures [35]. A growing body of evidence suggests that angioplasty is less effective than coronary bypass surgery, particularly in diabetic renal patients [36].

Congestive Heart Failure (CHF) and Cardiomyopathy

CHF commonly develops as a consequence of coronary disease and other types of organic heart disease. Although patients with renal

failure and ESRD are disposed to fluid accumulation on the basis of decreased capacity to excrete salt and water, pulmonary edema is unusual in the absence of decreased heart pumping function. However, the occurrence of flash pulmonary edema in the setting of relatively well preserved systolic cardiac function suggests the possibility of diastolic dysfunction or functionally significant bilateral renal arterial occlusive disease. A clinical diagnosis of CHF is associated with a > 60% increased mortality risk in ESRD patients.

For ESRD patients, PD is sometimes preferred over HD because of continuous UF and avoidance of continuous shunting of cardiac output through a vascular access [37]. PD is effective for controlling CHF symptoms and ventricular function [38] but it has not been clearly shown to be superior to other modalities. CHF management is centered on dietary restriction of salt and water and fluid removal through dialysis. Diuretic therapy is not usually helpful except for new ESRD patients who still produce urine or the occasional patient with preserved residual urine output. Afterload reduction with ACE inhibitors should be considered but may compromise residual renal function and dispose to hyperkalemia. Close monitoring is recommended when using these drugs. Digitalis preparations may be effective but the most common preparation, digoxin, is normally excreted by the kidneys, necessitating dose adjustment and close monitoring of blood levels in renal patients. As with any patient with CHF, the underlying cause of the pump failure should be explored and treated to the extent possible.

CHF indicates the presence of cardiomyopathy, broadly defined as a pathologic alteration of the cardiac muscle. Cardiomyopathy may also be manifest as arrhythmia or it may be subclinical. Several types of cardiomyopathy have been characterized in ESRD patients [39].

The high prevalence of CAD among ESRD patients gives rise to ischemic cardiomyopathy, manifest by regional wall motion abnormalities, decreased ejection fraction, and clinical symptoms and signs of CHF. Ischemic cardiomyopathy and regional wall motion abnormalites imply the presence of prior myocardial infarction. Angina may or may not be present, depending on patient characteristics and the presence of ischemic myocardium. Patients should be assessed for at-risk myocardium and possible revascularization. However, the risk of bypass procedures is generally elevated in patients with pump failure.

Dilated cardiomyopathy is characterized echocardiographically by increased chamber volume and decreased left ventricular pumping function. Typically, the left ventricular ejection fraction is < 40%. Patients may present with CHF or arrhythmia. Dilated cardiomyopathy appears to be distinct from ishcemic cardiomyopathy in that regional wall motion abnormalities are lacking and coronary artery disease may be absent. The etiology of the dilatation is unclear but may be associated with the uremic state or uremic toxins.

Hypertrophic hyperkinetic cardiomyopathy is characterized echocardiographically by thickened ventricular wall, normal chamber volume, and relatively preserved pump function. These patients are usually considered to have cardiac symptoms on the basis of diastolic dysfunction. Left ventricular systolic dysfunction and the CHF syndrome can arise as a late manifestation. Hypertrophic cardiomyopathy confers substantial mortality above and beyond hypertension. LVH is associated with CHF and arrhythmia is an independent risk factor for mortality. The pathogenesis of hypertrophic cardiomyopathy has been related primarily to hypertension [21] but factors such as anemia, obesity, valvular

heart disease, sympathetic overactivity, certain antihypertensive medications, and anemia may also play an important role [40 – 42]. These associated conditions should be identified and rectified to the extent possible. The complications associated with LVH should be addressed as required by clinical circumstances.

Arrhythmia

Cardiac arrhythmias are an independent risk factor in ESRD patients (Figure 1). Mild rhythm disturbances are extremely common in ESRD patients. When sought by Holter monitoring, ventricular and supraventricular arrhythmias were found in 30 – 90% of dialysis patients [43, 44]. The frequency of these largely assymptomatic arrhythmias increased during or following HD treatments. The prevalence of arrhythmias increased with age of the patient and longer duration of ESRD. Arrhythmias may be less common in continous ambulatory peritoneal dialysis (CAPD) patients than HD patients [45].

Arrhythmias can arise from electrolyte disturbances, as a reaction to the dialysis and UF procedure, and heart disease. More serious arrhythmias usually arise secondary to underlying organic heart disease. The relative risk of death is increased 51% in ESRD patients with a recorded clinical history of arrhythmias, without regard for the nature or success of treatment. Treatment should be initiated with pharmacologic, electrical, or surgical techniques as for non-renal patients. Drugs such a procainamide are normally excreted by the kidneys, necessitating careful dose adjustment and monitoring of drug and metabolite levels.

Cerebrovascular Disease

Cerebrovascular disease arises from the same metabolic, environmental, and genetic risk factors that promote atherosclerosis in other vascular beds. The prevalence of cerebrovascular disease of any type is approximately 16% in ESRD patients. Approximately 13% of deaths in ESRD patients are attributed to cerebrovascular disease. Among ESRD patients, the risk of death from stroke (as for other causes of death) is inversely related to the delivered dose of dialysis [46].

The clinical manifestations, diagnosis, and treatment of cerebrovascular disease are similar in the renal and non-renal populations. The major cerebrovascular syndromes are transient ischemic attack (TIA) and cerebrovascular accident (CVA). In addition, hemodialysis patients are susceptible to subdural hematomas, in part related to platelet dysfunction and regular exposure to heparin. The incidence of stroke is > 4-fold higher among ESRD patients than the general population [47]. Among ESRD patients, the risk of carotid atherosclerosis is associated with age, coroanry disease, and the plasma concentration of lipoprotein (a).

Carotid endarterectomy prevents subsequent stroke in patients with high grade carotid stenosis or symptomatic TIAs. However, patients with renal failure have been found to have poorer outcomes than non-renal patients in terms of operative mortality and subsequent stroke [48, 49]. At this time, an individualized assessment of risks, benefits, and patient preferences related to surgical intervention should be undertaken.

Peripheral Vascular Disease (PVD)

PVD is reported in approximately 36% of dialysis patients and is associated with increased mortality risk. The risk and pathogenic factors are fundamentally similar for PVD and CAD. Many of the important risk factors for atherosclerosis are commonly present in renal patients, including hypertension, diabetes, and a history of smoking. The problem may be compounded to the extent that renal failure independently promotes atherogenesis.

Dialysis patients experience the same clinical manifestations of PVD as non-renal patients including intermittent claudication, rest pain, and ulceration of the extremities. Physical findings may include diminished or absent peripheral pulses, skin atrophy, decreased hair growth, and ulcers. The diagnosis is confirmed and staged using non-invasive vascular studies and angiography. The lower extremities are preferentially affected. However, upper extremity arterial inflow is particularly important for hemodialysis patients with permanent vascular accesses in the upper extremities. It is likely that upper extremity arterial occlusive disease contributes to vascular access problems including failed maturation, low flow, thrombosis, and steel syndromes. Upper extremity disease that might otherwise be assymptomatic can manifest itself in HD patients in this way. Hand weakness, digital ulceration, and amputations can be unfortunate complications of the combination of upper extremity vascular disease and vascular access devices.

The treatment of PVD is graded to the severity of illness. Mild disease can be managed by life style changes. Smoking cessation will often yield some symptom relief. Elimination of medications that impede peripheral dilation should be considered. Patients with more advanced disease can be considered for revascularization procedures, either surgery or angioplasty. Many ESRD patients progress to amputation, particularly diabetic patents who tend to have microvascular disease that is not amenable to revascularization. PVD is a marker for increased cardiovascular morbidity and risk. Higher mortality has been reported for revascularization surgery than for primary amputation, suggesting the need to carefully select patients for aggressive revascularization procedures [48].

Hyperlipidemia and Hyperhomocysteinemia

The high prevalence of atherosclerotic vascular disease among ESRD patients is potentially explained by several prominent risk factors including hypertension, cigarette smoking, DM, and hyperlipidemia. A variety of lipid abnormalities have been described in ESRD patients including hypertriglyceridemia and low high density lipoprotein (HDL) cholesterol. The pathogenesis of these abnormalities is partly related to decreased lipoprotein lipase activity, possibly as a consequence of accumated cytokines and other toxins [50]. The independent association between lipid abnormalities and either cardiovascular complications or outcomes has not been extensively studied in patients with renal failure. Based on extensive studies in non-renal patients, hyperlipidemia should be sought and treated in ESRD patients but definitive proof of efficacy is lacking at this time.

Homocysteine is an amino acid that has been found to be associated with athero-

sclerosis in the general population. Homocysteine levels are substantially elevated in ESRD patients [51]. Hyperhomocysteinemia is associated with the low concentrations of folate and pyridoxine and exogenous administration of these vitamins appears to lower homocysteine levels.

Anemia

Some degree of anemia develops in the majority of patients with ESRD, often beginning in the pre-ESRD phase of renal failure. The predominant reason for the anemia of renal failure is erythropoietin deficiency. Erythropoietin is produced in the kidney and the synthetic capacity declines with progressive renal failure. In addition, direct bone marrow suppression and shortened red blood cell survival have been reported for ESRD patients. The HD procedure is also associated with mild blood loss although this has been minimized with modern techniques.

Anemia is associated with measurable differences in mortality and morbidity. A recent large observational study found that mortality risk was approximately 2-fold higher in patients with a hemoglobin concentration < 8 g/dL as compared with a concentration of 10 g/dL [52]. The majority of patients were being treated with recombinant human erythropoietin (rHu-EPO). The study could not reliably distinguish among the effects of anemia per se, rHu-EPO treatment, and comorbid conditions, such as infection, that might induce rHu-EPO resistance. Anemia was also associated with left ventricular dilation, clinical heart failure, and increased mortality [42]. The treatment of anemia with recombinant rHu-EPO was also associated with a reduction in hospitalization [53]. Anemia also influences individual patients as revealed by the effects of rHu-EPO treatment. The correction of anemia using rHu-EPO was associated with improvements in exercise capacity, oxygen consumption, appetite, nutritional status, and quality of life [54, 55, 56].

The anemia of renal failure is characterized by normochromic normocytic red blood cell morphology. rHu-EPO levels are inappropriately low for the degree of anemia but it is seldom necessary to measure hormone levels in order to make a secure diagnosis. In the absence of other causes of anemia or treatment with rHu-EPO, the blood concentrations of iron, ferritin, vitamin B_{12}, and folate are usually in the normal range. Patients exhibit variable degrees of fatigue and anorexia. The symptoms of any underlying cardiovascular disease may be exacerbated by anemia. However, the onset of the anemia is often so insidious so that the patient does not perceive the functional decline.

The treatment of anemia has been greatly facilitated by the availability of rHu-EPO. Current guidelines call for initiation of therapy at a dose of 80 – 120 U/kg/week administered as 2 – 3 doses. The subcutaneous (SC) route is probably more effective than the intravenous (IV) route. The goal of therapy is to increase hematocrit (HCT) to the range of 33 – 36%. Greater elevations may be associated with worse outcomes for unclear reasons. Iron deficiency often develops in rHu-EPO-treated patients due to the high degree of iron needed to support new erthropoiesis. Iron replacement therapy is usually required. Oral iron preparations are poorly absorbed and iv iron is usually required. Both intermittent replacement regimens and continuous maintenance regimens have been proposed [57, 58]; the ideal regimen remains to be established. Iron should be supplied to maintain the transferrin saturation > 20%. Additional response in

terms of HCT may be seen at even high iron levels but the serum ferritin should remain < 800 ng/mL to avoid iron toxicity. The response to rHu-EPO may be augmented by concomitant use of androgens (nandrolone decanoate) [59]. RHu-EPO responsiveness is also augmented by increased delivered dose of dialysis [56, 60]

Renal Osteodystrophy

Renal osteodystrophy in the broadest sense refers to the alterations in mineral metabolism and bone health associated with kidney disease. This complicated topic is discussed at length elsewhere. However, it is important to mention renal osteodystrophy in the context of comorbid conditions. The consequences of altered mineral metabolism extend beyond the direct features of bone disease, such as fractures, pain, and osteopenia. Altered mineral metabolism can lead to mineralization of soft tissues and blood vessels, and therefore contribute to functional alterations of virtually every organ system. Hyperparathyroidism has been implicated as a major uremic toxin. Altered mineral metabolism has been associated with a variety of clinical conditions and symptom complexes such as impotence, anemia, and weakness. Patients with markers of altered mineral metabolism have increased mortality. The wider implications of renal osteodystrophy and its treatment require further investigation.

Carpal Tunnel Syndrome (CTS)

CTS occurs more often among ESRD patients than the general population. The excess incidence of CTS is generally attributed to β_2-microglobulin (B2M) deposition within the median nerve sheath. The clearance of B2M is compromised in patients with ESRD. B2M deposition also contributes to bone pain and arthropathy. While CTS probably does not confer added mortality risk, it is a significant cause of morbidity, medical expense, and decreased quality of life.

Patients usually complain of numbness and parasthesias of the middle 3 fingers of the affected hand. Initially, the symptoms are worse at night and may interfere with sleep. As the condition progresses, it can cause weakness and muscle atrophy. The clinical diagnosis is confirmed by electromyography. The initial treatment for relatively mild disease consists of wrist splints and non-narcotic analgesics. Often, these measures are inadequate over time and patients will require surgical release of the carpal tunnel. Surgical results are usually highly satisfactory in well-selected patients. The development of CTS in the same hand as a patient's vascular access presents the risk of access failure in that arterial inflow must be mechanically occluded in order to achieve a bloodless operative field.

Infectious Diseases

Infectious deaths are relatively common in ESRD patients, accounting for 31% of deaths annually. The incidence of infectious diseases

is also increased in ESRD. Most infectious complications occur acutely while a patient is receiving dialysis. However, there are several chronic infections that may predate ESRD and can rightly be considered as comorbid conditions. The high infection rate in ESRD patients is attributable to both increased exposure to infectious agents and decreased host defenses. From the viewpoint of this chapter, comorbidity among ESRD patients consists of an increased prevalence of chronic infections and an increased risk of acute infections.

ESRD patients face numerous infectious exposure opportunities. HD patients are vulnerable to infection through the HD procedure which requires regular entry into the circulation. A common nidus for infection can be found in the synthetic materials that are often used for vascular access in the way of temporary catheters or synthetic bridge grafts. Blood products were a historically important source of viral infection although the risks and exposure have been dramatically curtailed by the advent accurate testing for blood borne viruses, hepatitis B vaccine, and rHu-EPO for treatment of anemia. For PD patients, the dialysis catheter affords an efficient mode of entry and the dialysis fluid a rich breeding ground for infections.

The infectious exposure opportunities are magnified by defects in host defense that arise as a consequence of the uremic syndrome. Multiple alterations in host defense mechanisms have been described. Compromised humoral immunity is seen by decreased immunoglobulin responses to specific antigen stimuli. Altered cell-mediated immunity is manifest by decreased delayed hypersensitivity and T cell proliferative responses to specific stimuli, decreased production of interleukin-2, and decreased T cell sub-populations. The role and importance of specific defects in immune function remains unclear. Furthermore, it is difficult to quantitate the role of increased exposure vs. decresed defenses in the high risk of infection among ESRD patients.

Infection control procedures are critical in the dialysis procedure to protect both patients and staff. Universal blood handing precautions must be followed. Blood transfusions should be minimized. When transfusions are required, rigorous blood screening programs should be in place. Native arteriovenous fistulas are preferred over vascular access devices that require synthetic materials, both from the viewpoint of infection control and longevity of the access. Much evidence suggests that synthetic grafts are used more than necessary in the U.S. Patients should be vaccinated against hepatitis B and pneumococcus, preferably prior to the development of ESRD. Increased dose or frequency of hepatitis B vaccine may be required for seroconversion of ESRD patients. In addition, ESRD patients almost always meet the accepted criteria for receiving yearly influenza vaccination. Many units isolate patients with chronic viral infections such as hepatitis B, hepatitis C, and human immuno-deficiency virus (HIV) although the value of this step is questionable if all other recommended precautions are followed.

The clinical manifestations of infection in ESRD patients are as protean as the possible sites and agents. Common infections include bacteremia, endocarditis, osteomyelitis, urinary tract infection, and graft infections. Peritonitis is common among patients treated with PD.

The specific treatment of infectious diseases should be tailored to the presumed or defined organism as well as patient characteristics. When infection is suspected based on fever or other clinical evidence, cultures should be obtained from potentially relevant sites such as blood and urine. However, empiric treatment of strongly suspected infec-

tions should not be delayed while waiting for cultures to grow as even transient bacteremia can lead to seeding of synthetic material, heart valves, or other sites. Dose or interval adjustments are needed for most antimicrobial agents including semi-synthetic penicillins, cephalosporins, aminoglycosides, vancomycin, rifampin, quinalones, acyclovir, and fluconazole. In addition, dose supplementation may be required following dialysis for certain agents such as vancomycin and aminoglycosides. Antibiotic clearance may be strongly influenced by dialyzer specifications. Blood level monitoring is valuable for certain antibiotics such as vancomycin and aminoglycosides. Antibiotic toxicity must be avidly sought and prevented. Although nephrotoxity seems unimportant once patients have reached ESRD, this may not be true for patients who still retain residual renal function. ESRD patients may be especially vulnerable to and affected by vestibular toxicity that can occur with aminoglycosides.

Other Comorbid Conditions

A number of other comorbid conditions are found in ESRD patients including chronic lung disease, smoking, and neoplasms (Figure 1). Although the prevalence of these conditions is relatively low, they are associated with increased mortality risk. Diagnosis and treatment are not materially different from non-ESRD patients.

Management decisions for some comorbid conditions require a judgement about the balance between the short-term risk of treatment and long-term outcomes. Physicians and patients must ask whether the natural history of ESRD justifies the risks of certain intensive treatments such as chemotherapy or bypass surgery. This is a difficult area in ESRD care without definite answers. Although the average survival for ESRD patients is relatively poor, there is tremendous variability and many long-term dialysis survivors exist. Furthermore, average population statistics do not easily translate to individual patients. Formalized decision analysis may provide a framework for discussion. Ultimately, such decisions require careful, individualized discussion of risks, benefits, and preferences among physicians, patients, and families.

Summary

The treatment of patients with ESRD entails both renal replacement therapy and the treatment of comorbid conditions that are associated with renal disease. Largely as a result of comorbid conditions, ESRD patients fare worse than the general population with regard to important clinical outcomes such as mortality, hospitalization, and quality of life. In describing ESRD patient outcomes, and resource utilization at any level, it important to account for variation in comorbidity, particularly for making comparisons. For these reasons, comorbidity is central to both clinical and epidemiologic considerations of ESRD.

Comment

Some of the data reported here were supplied by the United States Renal Data System (USRDS). The interpretation and reporting of the data are the responsibility of the author and in no way should be seen as the official policy or interpretation of the U.S. Government.

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Rehabilitation in Dialysis Patients: Reexamining the Barriers and Benefits

Tricia A. Thornton and Raymond M. Hakim

Introduction

Prior to the inception of the End-Stage Renal Disease (ESRD) Program in 1972, in the U.S. most patients chosen to receive renal replacement therapy (RRT) were considered very good candidates for rehabilitation. Indeed, this was a major requirement for acceptance into the dialysis program. Generally, these patients were working-age men who had few, if any, other comorbid conditions [18]. The decision to initiate the ESRD program was based in large part on the prediction that vocational rehabilitation would be a reality for patients covered by the program. An estimated 60% of patients were expected to return to work following “retraining”, and 40% were expected to continue their employment with no need for “retraining” [43, 63]. Certainly, the 80 – 90% employment rates reported by such early studies as Baillod, Crockett and Ross (1969) and Cameron, Ellis, Ogg et al. (1970) seemed promising [13]. Unfortunately, the current spectrum of patients receiving ESRD therapy is such that the goal of attaining paid employment as an index of rehabilitation is one that may not be or cannot be shared by a majority of these patients, especially those who are retired, choose to be homemakers, or have additional debilitating comorbid conditions.

With the median age of prevalent ESRD patients (i.e. on dialysis for $\geq$ 1 year) approaching the generally accepted retirement age of 65 years, the predominant inclusion of paid employment in the definition of rehabilitation becomes less appropriate. Needed is a more encompassing definition of rehabilitation as *the restoration of meaningful existence in the patient’s life*. Survey instruments measuring this"patient quality of life" are increasingly being viewed as central to evaluating the utility of the existing U.S. ESRD program, and employment status is only one of several factors influencing these measurements. Other non-traditional goals and yardsticks of rehabilitation aimed at improving the quality of life of patients on dialysis need to be considered including physical, social, psychological and intellectual rehabilitation [17, 71].

Patient quality of life has certainly been enhanced by improvements in the quality of medical care provided for RRT, allowing patients to have fewer adverse symptoms on dialysis and therefore greater potential for rehabilitation. These advances include:

– the use of bicarbonate instead of acetate as the base replacement, with substantial reductions in the symptoms of nausea and vomiting;
– volumetric control of ultrafiltration and sodium modeling, which have decreased the incidence of cramping and hypotension;
– the use of biocompatible and high-flux membranes with a decrease in first use reactions and incidence of infections and amyloid bone disease;

– improvement in water treatment with a decrease in the incidence of aluminum-induced bone and central nervous disorders;
– optimization of dialysate concentrations in terms of calcium concentration [73] and potassium concentration, resulting in improvement of cardiac contractility; and finally and more importantly,
– new medications, especially antihypertensives and recombinant human erythropoetin (rHu-EPO), to minimize drug side effects and anemia.

As a direct result of these major technological and pharmacological innovations, the dialysis community – including patients, providers and health care workers – is now poised to concentrate on ways to enhance patient quality of life that go beyond purely medical intervention. Mounting research literature examining quality of life issues point to exercise and other types of rehabilitation as methods to effect quantifiable improvements in patient quality of life. Perhaps even more consequential to engaging nephrologists and health care organizations are the correlations found in the relationship between rehabilitation, patient quality of life and traditional clinical outcomes. Rehabilitation when linked with patient outcomes is more likely to be endorsed and actively supported by providers as beneficial to patients and worth the commitment of their resources.

Increasingly, rehabilitation efforts which emphasize a more holistic approach to patient care are gaining acceptance among dialysis professionals and are being integrated into dialysis programs nationwide. To the extent that improved clinical outcomes positively impact financial performance, providers would be well served to investigate strategies, such as the implementation of targeted rehabilitation programs, to improve patient outcomes [72]. This chapter will summarize and highlight some of the most current research literature on quality of life and rehabilitation. In addition, because one of the greatest obstacles to rehabilitation is the lack of information in the hands of dialysis professionals as to how to create and implement targeted rehabilitation programs, this chapter will also offer a framework for the development of various rehabilitation programs.

Barriers to Rehabilitation and Links to Patient Outcomes

Inactivity

It may come as no surprise to many nephrology professionals that when Kutner, Cardenas, and Bower (1992) evaluated older patients' health outlook they found that,"fatigue was the most frequently specified reason given for activity limitation by the older [ESRD] patients interviewed" [44]. Patients who feel limited as to the type and amount of physical activity they can carry out may find themselves restricted as to employment options and the level of independence they can enjoy in daily living, both of which may contribute to decreased life satisfaction."In hemodialysis (HD) patients, the reduction of work capacity is aggravated by a lack of physical training (and), combined with inactivity during dialysis itself, leads to disuse atrophy. It is well known that inactivity, immobilization and bed rest all produce decreased muscle strength in healthy subjects" [44]. Thus, while fatigue can lead to decreased

activity, the opposite – that inactivity can lead to more fatigue – is also true. This lowered capacity for performing daily activities translates into patients becoming fatigued more easily and subsequently reducing their activity levels even further. Still, fatigue in dialysis patients is a problem which has received little attention and even less intervention over the past few decades. That is slowly beginning to change as health care professionals increasingly view the dialysis procedure not only as a life saving procedure, but as a necessary technique to allow patients the opportunity for meaningful existence in their lives.

Anemia

Insufficiently-corrected anemia, along with inactivity, contributes to the 50 – 60% reduction in exercise capacity experienced by most ESRD patients compared to their age and sex-matched peers. Anemia is also known to independently cause the ESRD patient to feel fatigued and lethargic. The introduction of rHu-EPO therapy in 1989 provided physicians with the means to significantly reduce anemia in most ESRD patients. However, with regard to the optimal level of hematocrit or relative red blood cell volume, there have been several artificial barriers in the investigation of the relationship between the potential for rehabilitation and higher levels of hematocrit (HCT). In the U.S. these barriers include the denial by Medicare intermediaries of reimbursement for rHu-EPO for HCT levels >36% except with medical justification, and the more recent decision by the Health Care Finance Administration (HCFA) to implement a 3 month hematocrit average target of 36.5% as a reimbursement cut-off without allowing for medical justification. Recently the HCFA has curtailed these restrictions by raising the 3 month target HCT to 37.5% and by allowing for medical justification. Thus, the impact of hematocrits > 36% – and therefore higher oxygen carrying capacity – on rehabilitation (e.g. exercise, cognitive function) cannot be adequately explicated at this time.

Still, it appears that the etiology of fatigue in this patient population often has several compounding factors, making its elimination more complicated than the appropriate utilization of rHu-EPO and the achievement of a target hematocrit."The use of rHu-EPO to increase [peak oxygen uptake] assumes that muscle is capable of extracting all the increased oxygen delivery." Because uremic myopathy may be limiting peak oxygen uptake, increasing the intrinsic oxidative capacity of skeletal muscle through exercise training may also be necessary to increase oxygen consumption and improve physical functioning [2, 53].

Depression

There is evidence that fatigue in dialysis patients may at times have psychological causal components as well. Even among some ambulatory patients with good muscle strength, fatigue was found to be a significant problem, indicating that muscle fatigue alone could not fully account for the problem. Cardenas and Kutner demonstrated a correlation between fatigue and depression in ESRD patients, particularly in those patients for whom the fatigue was worse upon rising and improved during the day [7]. Fortunately, it is not essential to know the underlying cause(s) of fatigue in a particular individual since exercise training has been demonstrated as successful in reducing fatigue regardless of whether the source is physiological or psychological.

Late Initiation of Dialysis

Another important barrier to rehabilitation is the delay in timely initiation of patients on dialysis therapy. This is a multi-factorial problem that may result either from late referral of the patient to nephrological follow-up, or the late referral of patients by nephrologists to definitive therapy. Traditionally, patients were initiated on dialysis when they became symptomatic (e.g. persistent nausea and vomiting, congestive heart failure (CHF), or neurological obtundation). However, there is increasing evidence that patients starting dialysis in a debilitated state are much more refractory to rehabilitation, both physical and psychological. More recently, the concept of"healthy start" of patients on dialysis based on an objective nutritional evaluation of appetite and protein intake has been advocated [29, 35] and appears to be important in the outcome of ESRD patients, particularly peritoneal dialysis (PD) patients. Such a"healthy start" also presumes that these patients may be more likely to have native arteriovenous (A-V) fistulas, which are generally associated with significantly less morbidity and therefore improved rehabilitation potential.

Lack of Patient Education

Coupled with this late or symptom-driven start of dialysis has been an inadequate attention to the education of the pre-ESRD patient as well as the patient already established on dialysis. Bremer et al. found that a patient's sense of"control over non-health aspects of life, such as work or community affairs," correlated with the perceived ability to adhere to medical regimen and with good psychological adjustment to ESRD [6]. Rasgon et al. showed that pre-ESRD patient counseling can increase the likelihood that a working individual stays on the job after beginning dialysis, which may help the patient maintain the level of quality of life he or she enjoyed prior to RRT [61]. These studies suggest we should be targeting the chronic renal failure (CRF) patient early in the disease process for participation in a comprehensive education program, which empowers and encourages the patient to maintain control over non-health aspects of their lives, thereby enhancing their perceived ability to comply.

By comparing patients who were randomly assigned to receive either an"enhanced" pre-ESRD education or the"standard", or minimal, pre-ESRD education, Binik et al. demonstrated that an enhanced pre-ESRD education program can delay the need for RRT by an average of 4.6 months [4]. Bremer et al. found that the ESRD patient needs to feel that someone – a health care provider, a family member, the patient himself – is in control of his or her health care [6]. For the patient to perceive that medical treatment outcomes are random or arbitrary would mean poor psychological adjustment to the illness. In this context, it is interesting to note that Sehgal et al. found that the patient's perception of his or her own nutritional and dialysis adequacy was in many cases inconsistent with the objective measures of serum albumin concentration and *Kt/V* [67]. The findings of each of these studies emphasize the need for dialysis providers to educate patients as to how dialysis treatments, nutrition, access care, and other issues directly affect their health and how traditional medical indicators accurately reflect adequacy. Patients have a need to know that their own medical outcomes are not arbitrary and that their efforts to receive adequate nutrition and dialysis can and do improve their overall health and well-being. This knowledge in the hands of patients can have a lasting positive impact on their medical and psychosocial outcomes.

In addition to improving clinical outcomes, patient education can also positively impact other consequential outcomes such as patient satisfaction and a provider's financial well-being. Managed care organizations (MCOs) and, more recently, the HCFA have begun emphasizing patient satisfaction as an important measurement of quality of care. Providers are increasingly expected to deliver care which not only produces good medical outcomes but also results in the patient feeling satisfied with the overall health care experience. In light of this, it is worth noting that Schauffler, Rodriguez and Milstein found that"patients who reported that their physician or other health care professional had discussed one or more health education topics with them in the last 3 years were more likely to be very satisfied with their physician than were patients who reported that they had not" [66]. Therefore, the more effectively a provider educates patients, the more successful it may be in securing managed care contracts, which in the future could prove critical to its survival in the health care industry. Bartlett advanced yet another financial motive for the development of patient education programs [3]. He summarized studies on the cost-effectiveness of patient education in various health care settings and found"on the average, for every dollar invested in patient education, 3 – 4 dollars were saved." Clearly, the nephrology community could be doing a better job for the patient by focusing more time, effort and resources on patient education.

Rehabilitation Programs

When looking to develop a rehabilitation program, one must first recognize that rehabilitation requires the full participation of the patient. Patients must be able to foresee *meaningful* benefits as a result of participating in a rehabilitation program, and what is meaningfully beneficial to one patient, may not be to another. This has more to do with the patient's personal values, goals and interests than with the fact that he or she is a dialysis patient. Meers et al. demonstrated notable discrepancies in evaluations of patient quality of life between health care providers and the patients themselves, with providers consistently underestimating the adaptive capabilities of dialysis patients [52]. Hence, the participation of the patient in the initial planning stage is essential. A program designed predominantly by the health care provider might not only be inappropriate but most likely unsuccessful because the desired ends might not be shared by the patient. On the other hand, a patient often needs the guidance and support of his or her health care provider in setting progressive, realistic goals. In fact, according to the Life Options Rehabilitation Advisory Council, staff encouragement of the patient has been shown vital to patient perseverance and to the ultimate success of all rehabilitative efforts. With this in mind, it is ideal to be able to offer patients a variety of rehabilitation programs from which to choose with ample information on how each program may enhance their quality of life. Some program options are presented in the remaining sections of this chapter.

Physical Rehabilitation

For several decades numerous studies have demonstrated the benefits of exercise training in the general population and in various disease populations. It was not until the early 1980s, however, that the first few articles examining the benefits of exercise training in dialysis patients were published [8, 22, 24, 28, 74]. The results were encouraging, showing that ESRD patients receive physical and psychological benefits similar to those in other populations. In fact, the more debilitated the person was, the more he or she benefited from the exercise training.

Physical work capacity as measured by the graded exercise treadmill stress test and peak oxygen consumption improved by 20% on average following exercise training. Increases in HCT and hemoglobin concentrations were also associated with exercise training, and later (post-rHu-EPO) studies indicated that exercise training may play a vital role in maximizing the potential benefits of rHu-EPO therapy in correcting anemia [53, 70]. Hypertensive patients were able to control their high blood pressure with reduced doses of antihypertensive medications. Diabetic patients experienced improved sensitivity to insulin as evidenced by lower fasting insulin levels. Resultant improvements in coronary risk factors such as triglyceride and cholesterol levels may further translate into decreased risks for morbidity and mortality [22, 23, 24].

The psychological benefit of exercise training was demonstrated by reported decreases in anxiety and depression. Those patients experiencing the more severe clinical depression received the greatest benefits [8, 9, 22, 23]. Patient quality-of-life issues, such as patient outlook for the future and levels of social interaction, were also observed as improving after exercise training. For the patient who was very active prior to renal disease, the restoration of one's physical strength and ability means the recollection of those aspects of one's life which are of great importance and meaning. Again, the focus should be on what it is that the patient wants to be able to do as an outcome of the physical rehabilitation process and the program should be tailored to the particular challenges the patient faces in achieving his or her goals.

One way to most effectively involve patients in a physical rehabilitation program (Table 1) is to offer an in-center exercise program in which patients may participate while on dialysis. The Amgen-sponsored Life Options manuals on designing an exercise program are excellent sources to model. Compliance is improved because staff can approach exercise as an integral part of the patient care plan, which is expected to be performed during the time spent at the facility. A well-organized in-center exercise program requires little additional effort on the part of nurses and patient care technicians. An initial assessment and follow-up of patients participating in an exercise program by an expert in exercise physi-

Table 1. Examples of Physical Rehabilitation

Aerobic exercise training
- Cycling or pedaling during dialysis
- Walking with other patients or staff
- Hiking with outdoors club
- Swimming at rehabilitation/recreation center

Strength/flexibility training during dialysis
- Range of motion exercises
- Leg lifts
- Hand grip exercises
- Arm curls/extension with weights
- Wrist strengthening with weights
- Ankle strengthening with weights
- Arm exercises with stretch bands

ology is also helpful. In general, an atmosphere in which physical wellness and fitness is encouraged and supported can go a long way toward helping patients who desire to be physically rehabilitated succeed in their efforts.

Social Rehabilitation

There are many patients who are isolated from their friends and families and are, therefore, lacking in social support. This often results from the time they need to spend on dialysis and transplantation to and from the center, as well as from the fatigue experienced after dialysis. Rehabilitation of such a patient can vary from participation in a patient support group to involvement in a community project or organization with interests or concerns similar to those of the patient. Some patients may find joining an arts and crafts class very enjoyable while others may find volunteering at their local homeless shelter or at a community day-care center extremely rewarding. This may also involve vocational rehabilitation to a large degree, bearing in mind that a vocation is certainly not limited to paid employment. Some positions, paid or volunteer, require training or experience which can be acquired by attending classes or seminars or by initially working in other similar positions requiring less experience.

Every patient – every person – has a particular personality and a way of interacting with others, and each may enjoy any number of social activities available. The challenge is to help the patient discover what choices are available to him or her and to provide more than the necessary encouragement and support to get involved. Often patients and health care providers tend to see only the barriers to rehabilitation and so in an effort to protect themselves or their patients from disappointment they refrain from setting what they believe might be inflated expectations. However, Carney et al. noted that staff can make a difference by not fostering an environment of dependency but rather one of personal independence and responsibility [8]. Patients respond by adopting a more internal locus of control, enhancing feelings of empowerment.

One way to provide an opportunity for social interaction among patients is to establish a patient services committee made up mostly of patients as well as a few staff members. Patients plan and organize fund-raisers for a patient services fund which is used to enable a patient to receive medications not covered by insurance which he or she cannot afford, to fund festive seasonal events within the facility for patients, and to purchase games, exercise equipment or other items the committee deems acceptable. Patients may also participate in educational events sponsored by the National Kidney Foundation (NKF) called “People Like Us Live” which allow them to share their experiences regarding kidney disease with new renal patients and their families. Other programs facilitating social rehabilitation include adult day-care programs, story-tellers’ meetings and outdoor recreation groups (Table 2).

Table 2. Examples of Social Rehabilitation

– Patient services committees
– Arts and crafts classes within community
– Volunteer work at community shelters
– Religious group meetings/activities
– NKF “People Like Us Live” educational panel
– Outdoor recreation clubs
– “Story-Tellers" organization
– In-centerbBingo games among patients
– In-center arts and crafts activities

Psychological Rehabilitation

This type of rehabilitation could be as serious as making sure the severely depressed patient is referred to a competent psychiatrist or psychologist or as simple as providing the anxious patient the opportunity to discuss what is on his or her mind. Proper screening and diagnosis of depression or other preexisting psychological disorders such as schizophrenia are vital to addressing these issues. Patient care staff not trained to provide therapy should never be put in the position of having to address such problems but, rather, should notify the patient's attending physician of the possible need for professional psychological treatment. Still, there are a number of patients who, although free of specific psychological or psychiatric illness, suffer alterations in mood states ranging from depression to anxiety which affect their overall happiness and well-being.

For many of these people the chance to talk their problems out with someone else, or the suggestion to write down their concerns on paper as a cathartic measure, is a simple but helpful tool in the formidable task of coping with what life has dealt them. Patient support groups are a great way to facilitate ongoing therapeutic discussions and to have patients educate each other on coping skills which have worked well for them. They can be held once a week in the clinic at times which are most convenient for those patients who express an interest in participating. Also, patients may take advantage of support groups which the NKF organizes within communities on a regular basis. A support group which is well-structured and has a safe, supportive environment can be beneficial in helping patients adjust psychologically to their illnesses, thereby improving their psychological well-being and their quality of life.

Intellectual Rehabilitation

For many people their lives have largely been full of intellectual endeavors, and what means most to them is the ability and the opportunity to continue to engage in intellectual discourse or in an intellectual enterprise. For these patients, the first and most basic barrier they face is the elimination of uremic symptoms which can include confusion or decreased cognitive capacity. Beyond these issues of adequate dialysis, obstacles include loss of employment or other ties to intellectual pursuits such as involvement in educational, professional or political organizations. Often such losses happen during the few months prior to or during the initiation of dialysis; therefore, predialysis education for patients diagnosed with ESRD who are"approaching" dialysis is critical. Suspension, as opposed to discontinuation, of employment or other activities can provide patients with the needed interim for improvement in their health by dialysis or possibly transplantation, and early intervention should involve educating patients to this effect.

There are many patients, particularly younger persons, who desire to receive intellectual rehabilitation in the form of formal education – earning their GEDs or their undergraduate, graduate or professional degrees. Dialysis facilities can work with state rehabilitative services to provide patients with basic information and application assistance for schools and colleges offering classes at their specific level or on a specific topic of interest. Also, some adult education depart-

Table 3. Examples of Intellectual Rehabilitation

– Continued career work
– Participation in political organizations
– Participation in adult education or GED classes
– Participation in book clubs
– Participation in educational or professional organizations
– Participation in undergraduate or graduate college courses
– Participation in chess clubs
– Working in tutorial programs
– Participation in national organization meetings (AAKP, NKF, etc.)
– Writing in clinic newsletters

ments will either teach classes or offer tutorial services at the patient's dialysis facility. Again, the idea is not to do things for them but instead to give them the tools, the encouragement and the opportunities they need to accomplish on their own what will make their lives meaningful. Just as there are many social organizations accessible in our communities, there also are numerous organizations which may employ patients intellectually; in fact some may provide both intellectual and social involvement. Chess clubs, book clubs, and volunteer tutorial programs are some examples of associations in which patients can become involved (Table 3).

Conclusion

While there remain several barriers to rehabilitation for dialysis patients, the potential for rehabilitation in this patient population has never been greater, and care providers' efforts in developing rehabilitation programs should parallel this increase. A new focus on individualized patient goals promises to increase the success of a wide variety of rehabilitation programs. Research correlating rehabilitation and improved patient outcomes is significant and warrants action. A more holistic approach to caring for dialysis patients, in which rehabilitation is a major component of total health care, should function as an integral part of a well-constructed plan to achieve improved clinical outcomes and enhanced financial performance. However, recognizing the importance of valid quantitative data in gaining the support of nephrologists, providers and health care organizations, more studies are needed, particularly in the areas of psychological and intellectual rehabilitation, for which most of the information available involves a limited number of subjects.

Acknowledgment

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Ethical Decision Making in the Care of the Patient with End-stage Renal Disease (ESRD)

David C. Lowance

Ethical decision making in caring for patients with ESRD shares many common elements of ethical decision making with other areas of medicine. There are features unique to the patients with ESRD, however. Because of the frequent complexity and finality of the decisions both patients and nephrologists are asked to make, guidelines have been established to add some uniformity to the thought and advice we are asked to share with patients and their families. These will be reviewed.

Areas of Commonality

Common principles of ethical decision making for all medical care include the following:

- beneficence: defined as doing what is best for the patient,
- nonmalfiecence: defined as doing no harm to the patient,
- patient autonomy: defined as allowing the patient to determine for himself what is best, and
- justice: defined as evolving what is a proper balance between the patient and the environment in which he lives.

Areas of Differences

Features of care for the patient with chronic renal disease which are unique include following:

- the chronicity of survival by artificial means,
- the complexity of the patients' diseases,
- the fact that the burdens of treatment may often outweigh the perceived benefits of treatment, and
- the long-term physical, emotional, and financial cost to the patient, his family, and society.

In establishing guidelines to assist us in advising patients as to for whom dialysis should be considered or in helping advise patients when it is appropriate to consider withdrawal of dialysis, it is important to remember that the guidelines are consensus guidelines evolved from numerous discussions, conferences, and many hours of thought on the part of many people. Although not perfect, they represent an attempt to bring some uniformity to an area of care that has evolved as a result of technology that arrived and was widely implemented before anyone envisioned that its availability might not always be in the best interest of the persons to whom it would be provided.

Ethics and How We React

Ethics is defined as the discipline of dealing with what is good and bad, or right and wrong, or dealing with moral duty and obligation [1]. This definition, in and of itself, allows us to understand the complexity or the situation. None of us knows for certain what is necessarily good or bad, or right or wrong for another person. We certainly might have an opinion about what is right, but we do not know for certain. We have varied opinions regarding moral duty and obligation. Likewise, people's perceptions of life quality vary enormously and when facing the choice between prolongation of life by artificial means vs. imminent death, feelings are tense. Caregivers need to always consider the varied opinion of what is right and be mindful of the emotional intensity of the situations in which we are participants. We are there to give advice as to what can be offered, the projected outcomes of the therapies, and the consequences of the therapies, both good and bad. We are there to offer comfort and support to the patient while he makes the decision, and then we are there to make his decision work in the best manner possible. We are not there to make the decision for the patient. My perception of our moral duty and obligation is that we are there to educate the patient to a level of understanding that allows him to make an appropriate decision for himself. It is then our moral duty and obligation to help make that decision work even if it is different from the one we might have made.

Frequently, we as caregivers feel we have insights that patients do not have. Because of the intensity of what we do, the finality of death, and the awareness that we have the ability to prolong life, we often feel patients do not have the appropriate background to allow them to make the proper decision and thus have a tendency to transfer our feelings of what is right and wrong to them. In my opinion, this is inappropriate. What is appropriate is to educate patients so they make a shared decision with us. This shared decision making is equivalent to informed consent and is a primary goal of ethical decision making in any medical environment.

Evolution of Ethical Decision Making

We concede that defining what is good and bad for another individual is frequently difficult if not impossible. It is equally clear that our collective perceptions of what is good and bad, right and wrong evolve and change as our understanding of our environment changes. Therefore, what we may perceive as right today may be perceived as wrong tomorrow. The decisions each of us make as individuals with our patients daily, however, will when added together decide what decision society eventually makes for itself regarding what is right and wrong. This is the process by which guidelines evolve and policy is determined. The "right to life" issues, living wills, decision making regarding initiation and cessation of dialysis are modern inquiries that did not exist in the pretechnologic era. Collectively, we are still evolving our perception regarding what is right and wrong about these issues. Likewise, the rightness and wrongness of genetic engineering is an area evolving as our understanding of the potential consequences of genetic engineering expands. The choices we are currently making with individual patients will eventually evolve into policy and alter our future perceptions of what is best.

We need to view this ethical evolution as critically as we view our technologic advances. Science evolves by isolating under experimental conditions a particular process so the investigator can observe what nature already knows. By understanding the particular process, the investigator can add this observation to a greater body. Collectively, science, through understanding, can utilize the information to advance itself and hopefully benefit mankind. Likewise, each of our individual decisions with patients should be viewed as a rigorous scientific endeavor in which we and the patients are the natural reactants in the experiment. We are to provide to the patient new information that allows him to realistically understand the outcome of his actions and collectively these *patient made decisions* will determine our evolving policy. Recent practical examples of how juxtaposed technologic and ethical evolution occurs could be considered the advice modification we give patients with regards to survival quality on dialysis before and after the introduction of erythropoietin or advice given to diabetic and systemic lupus erythematosis patients with regards to their chance of survival with transplantation. In both instances, we are able to "upgrade" the potential outlook for the patients as we advise them as to what we feel are appropriate choices.

Despite the technologic advances, however, we are still confronted with patients for whom we know our current treatment may not offer quality survival. These patients constitute a major dilemma for all and consume an enormous amount of our emotional energy. Again, none of us is empowered to make a decision for another unless we are the legal surrogate for the patient. Our duty remains to educate these patients about what realistically can be offered and expected. When, in our opinion, our treatment does not offer realistic quality survival, we have an obligation to communicate this opinion to the patients. During the same encounter, we are obligated to inform the patient and family that care will be continued in a compassionate manner whether or not technologic intervention is utilized. Historical guidance for appropriate care in this situation has been present since Hippocrates [2] implored us to alleviate the sufferings of the sick and Francis Bacon urged we treat patients' symptoms only when they might recover [3]. In my opinion, it is only right that we tell patients what to expect and it is our moral duty and obligation to care for them, including the alleviation of suffering, if they choose not to initiate or to withdraw from dialysis.

Guidelines

Because of the enormity of cost, the frequent uncertainty of outcome, the finality of withholding dialysis, and varied opinions as to what is best, the National Kidney Foundation (NKF) set about to establish guidelines for us to use in having discussions with patients. These guidelines have evolved from a series of meetings with medical professionals, legal experts, clergy, ethicists, patients, and academicians. They are not intended to be rules and regulations, but are intended to be utilized as tools in discussing dialysis initiation and withdrawal with patients. The guidelines are based upon the recommendations of the Panel on Initiation and Withdrawal at the NKF Controversies in Quality of Dialysis Care Consensus Conference in 1994 [4].

Recommendation Summary

1. Decisions on whether to initiate or withdraw dialysis therapy are patient specific and

culturally, religiously and ethically sensitive decisions. These decisions can only be made on an informed basis by the individual patient/surrogate after consultation with the care team and others.

Comment: It is imperative to remember that as healthcare providers, the only unique elements we possess are technologic knowledge and our medical experience. The patient's cultural, religious, ethical values and traditions have as much validity or more than our own. If he is taught to incorporate our technical knowledge and medical experience into his body of information, he will make an appropriate decision for himself.

2. It is unethical to use mandatory standards including a patient's age life expectancy, quality of life, intellectual or physical limitations, socio-economic status or psychological condition in determining whether to initiate or withdraw dialysis.

Comment: All of these issues should be discussed with the patient and family. Certainly, life expectancy needs to be considered and discussed. However, none of these conditions should be used as a mandatory means of exclusion. The issues frequently arise in the consideration of patients for transplantation where there is a shortage of organs for transplant. Even in this setting, it is inappropriate to adopt mandatory exclusion criteria. It is appropriate to advise patients who are elderly or patients with severe coexisting illnesses that certain forms of therapy may be burdensome and ill advised.

3. The patient's values, preferences and goals are major factors, but not absolutely controlling, in the decision making process regarding initiation or continuation of dialysis. While the patient/surrogate has the right to request the initiation or continuation of dialysis treatment, the physician has the right to request the right to refuse to provide treatment which in his/her best professional judgment is the medically useless or futile and unwarranted; for example, where the patient is in a persistent vegetative state or is suffering from severe, irreversible dementia.

Comment: Preservation of patient autonomy is a major goal in ethical decision making. However, in any shared decision different participants may seek autonomous control. If autonomy is the goal of the process, there may be 2 separate decisions. If autonomy is viewed as a constraint, however, a shared common decision may be reached allowing each participant to feel his autonomy has not been violated by the other. In the current health care arena, there is, a third party, society, whose autonomy must be considered. Society, via monetary constraints, is expressing its position loudly. If all 3 participants decide a common goal is the best and most compassionate care for both individuals and majority, dialogue may allow this goal to be achieved. These guidelines represent an attempt to add uniformity to this quest.

4. A patient who has the capacity to make his/her own medical decisions has an absolute right to make a decision not to initiate or to withdraw dialysis therapy. His/her decision in these circumstances should be controlling.

Comment: The right of patient refusal has been upheld by the courts on numerous occasions. We have a duty to do everything possible to help patients understand why we think our therapy is best or not best for them. We do not have the right to force them to receive the therapy if, after proper endeavors, they still do not wish to proceed with therapy. This has to be viewed as an educative process.
We are obligated to improve our education skills to the highest level to optimize the patients' understanding.

5. If quality of life or level of mental functioning is used to justify a decision not to initiate dialysis or to withdrawdialysis and the patient has the capacity tomake medical decisions, it is only the patient's perception of his or her quality of life or level of functioning that should be utilized.

Comment: It is often useful to ask patients and families if they would like a therapy utilized if it would allow the patient to return to a quality of life consistent with what he had in the past or would want in the future. This situation frequently arises acutely when the patient is unable to speak for himself. The guideline serves 2 purposes:

– It allows all of us to realize it is the patient's perception of quality of life that is important.
– In the acute setting, this guideline helps the patient, family and/or surrogate to differentiate between the advisability of an acute intervention vs. a chronic intervention and allows the patient, family and/or surrogate to make a more comprehensible decision regarding what might be best.

6. Use of medical treatment, including dialysis, is not legally or ethically required where the patient will receive no substantive benefits from such therapy.

Comment: Again, this protects physician autonomy but encourages out of necessity the education of the patient about realistic expectations and outcomes. It also reverts back to the admonitions of Hippocrates and Bacon. Frequently, second opinions regarding the futility of a contemplated treatment will help patients understand complex issues.

7. In circumstances where a patient with ESRD is being evaluated for initiation of dialysis, it is recommended that dialysis be withheld where the patient:

– *a: is adequately diagnosed to be in a persistent vegetative state.*
– *b: has an irreversible and severe mental disorder that results in the patient being unable to react to or interact with his/her environment (e.g. advanced Alzheimer's disease or severe stroke).*

Comment: The key phrase in this guideline is "adequately diagnosed". Nothing breeds distrust of our profession more than authoritative advice given to patients when our basis for the certainty of the diagnosis is based on soft data. When advising against dialysis in the above setting, it is imperative to know the patient has an irreversible condition.

– *c: is expected to die within 60 days from a primary, non-renal disease, unless the patient has an overriding short term life goal that could be met by initiation of dialysis therapy.*

Comment: We are all terminal. The arbitrary number of 60 days is a guideline. Certainly, patients with longer life expectancies but with painful comorbid conditions may be advised against initiating dialysis. The use of dialysis for the achievement of short-term goals is very reasonable.

8. In cases where the benefits and burdens of initiation of dialysis for the patient are unclear, it is appropriate to recommend a trial period of dialysis of approximately 30 days.

Comment: Again, the quality of life issue is addressed. Frequently neither the caregiver nor the patient, family and/or surrogate knows what is best. A trial period is sometimes needed in order for us all to be educated.

9. A reassessment of all patients initiated on dialysis is appropriate after approximately 90 days of dialysis.

Comment: We have all encountered outcomes we did not predict. It is very appropri-

ate to counsel all patients preemptively that a trial of dialysis is just that. It is a way of giving permission to someone to change his mind. We all need that permission.

10. In circumstances where a patient is on dialysis, it is recommended that dialysis be withdrawn for a patient:

- *a: adequately diagnosed to be in a persistent vegetative state.*
- *b: with an irreversible and severe mental disorder that results in the patient being unable to react to or interact with his/her environment (e.g. advanced Alzheimer's disease or severe stroke).*

Comment: Natural circumstances frequently dictate that a decision made under initial conditions might be different from one made under new conditions.

11. In cases where the patient/surrogate is considering or desires to withdrawdialysis and the health care team believes that there are possible interventive measures which could reverse the patient/surrogate's desire to withdraw, it is appropriate to recommend a trial period of 30 days, or such time as is necessary for an assessment of the effectiveness of the interventive measures.

Comment: This recommendation allows for the same latitude of uncertainty that exists frequently when dialysis is contemplated initially.

12. There are no Federal or state laws or judicial decisions which permit the health care team and/dialysis facilities to unilaterally withdraw dialysis therapy from a patient who is abusive, persistently disruptive or "non-adherent" with his/her dialysis regimen.

Comment: Abusive people exist everywhere. We are not allowed to care exclusively for people who are nonabusive. We do have our rights however. Appropriate disciplinary care for the abusive patient is within our rights. Withdrawal of care is not. It is also inappropriate for one individual to jeopardize the care of many because of the individual's abusive behavior.

13. The medical personnel treating the patient have continuing responsibilities to the patient/others after a decision is made not to initiate/withdraw dialysis therapy.

Comment: Hippocrates and Bacon would be proud of our remembering their admonitions.

We, as individuals and as a society, are in an evolutionary process. Since we are a part of nature ourselves, it is appropriate to view ourselves as unfinished parts of a greater whole that will continue to evolve to a more finished product. The development of guidelines, based on ethical decision-making principles for care of patients with ESRD, is an appropriate manner in which to continue this process. It is also clear that the guidelines will change as technology advances and our understanding of the consequences of new technology advances.

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Administrational and Organizational Aspects of Dialysis

Theodore I. Steinman

Introduction

Driving forces in medicine and health care will impact on the approach to the administration and organization of dialysis units. Some of the issues which must be addressed (and will be discussed in detail) include the following:

- cost containment and managed care,
- corporatization of dialysis,
- changing role of government,
- shift of Medicare secondary payment (MSP) from 18 to 30 months,
- workforce: number of nephrologists who will be available to care for the end stage renal disease (ESRD) population and the impact this will have on requirements for other members of the health care team,
- accountability (for physician performance, measures of quality and outcomes),
- consumer expectations/patient satisfaction,
- technology,
- patient care technologies, and
- data management and information/communication technologies.

When problems occur in patients with chronic illness, especially ESRD, the root of the problem is usually faulty systems rather than faulty physicians. With this background it is imperative that an excellent total delivery system be in place that ultimately results in quality of care for the dialysis population. Organizational flow diagrams may look good on paper, but the essence of success relates to completion of tasks and communication among those involved in care of the patient. General Dwight D. Eisenhower stated during World War II that before the battle is joined, plans are everything, but once the shooting begins, plans are worthless [1]. While plans are essential, only execution of those plans is what matters. Therefore, there has to be a clear understanding of everyone's role in a defined system and what responsibilities each person must fulfill. Completion of tasks is the bottom line and this necessitates all personnel being empowered to "own" part of system. There has to be a "buy in" by everybody involved for success to occur. Unless every member of the health care team can easily communicate with each other, problems will arise.

When developing the ideal organization/administration, new ideas need to be brought forth. Change will require new attitudes and there will be a need to embrace ideas that are foreign to us from a 1990's perspective. Differences will be noted if the dialysis unit is an independent facility or part of a large chain. The direction of the future is that alliances and networks will supercede the autonomous facility. Facilities belonging to national companies will require more uniformity in order to effectively address the issue of quality of care.

Practice guidelines, standards of care and algorithms will drive any new system and "free lance" approaches will not be tolerated because of the necessity to demonstrate proficiency that is mandated at both the regional and national levels.

Where is Managed Care Heading?

Changes occurring in medicine as a result of the rapid onslaught wrought by managed care have resulted in a shift from the previous laissez faire attitude (otherwise called fee-for-service reimbursement methodology).

Despite rising public criticism, managed care enrollment has continued to grow. In 1996, Medicare health maintenance organizations (HMOs) grew nearly 36% and Medicaid managed care membership rose by 58% [2]. In some markets, however, HMO enrollment has peaked or even declined. In markets like Boston, Cleveland and Los Angles, HMO membership enrollment dropped by 3 – 5% in 1996.

Market penetration for HMOs has now reached more than 50% in 10 major US cities. Forty-five percent of the nation's HMO members are enrolled in the 10 largest plans, an expression of the ever increasing consolidation. HMOs had decided to sacrifice growth for higher profits by raising premiums. More enrollees at lower premiums does not generate savings. Price hikes that are too high, however, have created openings for provider-sponsored HMOs and direct contractors.

Negative publicity generated by HMOs' focus on cost, cost and cost as the top three issues in health care has created a window of opportunity for physicians to take charge of every aspect of the health care delivery system. Payors and providers will now work in concert and replace the near-adversarial relationship that currently exists [3]. Quality of care, access to such care and cost effectiveness of the total delivery system will be the yardsticks to measure success.

Fundamentals for a Successful Dialysis Unit

There must be a commitment to high quality, cost-effective and ethical renal care. Recognition and respect for the multi-disciplinary nature of the health care team is an essential backdrop for success. Professionalism must exist at all times, the guiding principles being honesty, integrity, accountability and commitment to scientific principles.

Organizational charts will need to reflect the goals of care and we need to create a system that maximizes responsibility in delivering quality care. When asked about his success as a battlefield commander, General George Patten stated, "when going into combat I told the troops what needed to be done, not how to do it" [1]. In essence, micromanagement does not work. Let qualified personnel come up with the solution to challenges and dilemmas. Accountability will be required for every member of the health care team as well as the patient. Patients will need to know what they must do to participate in the system.

Nephrologists will need to make the necessary transformation from clinician to manager by acquiring specific business skills or forgo a large segment of overall decision-making in the dialysis unit. A combination of clinical acumen and understanding systems management will be critical to participate as a major

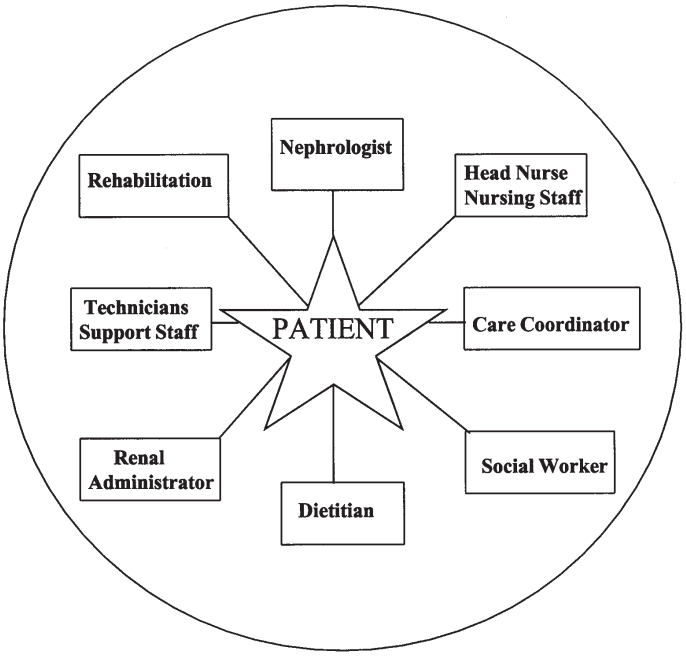

Figure 1. Circular integration: How the health care team relates to the patient in an integrated manner. The patient is the center of hub and all efforts are directed to improving quality of care and life. All members of the team coordinate care to achieve the desired goals.

player on the health care team. Credentialling of nephrologists in their new paradigm may be necessary so as to demonstrate effectiveness and value in the structure of the future. Corporatization will slowly envelop all of medicine, and nephrology will be in the forefront of change because of our longstanding history of government regulation and reimbursement via the monthly capitation payment (MCP) for care of the chronic dialysis patient.

It is imperative for every organization to create a vision and develop a mission statement. This mission statement should be the guiding principle by which all participants in the dialysis process should be held accountable. Vision should include the goals of organizing and coordinating the care of all patients within the defined population to enhance quality of, access to, and cost of renal care.

The mission statement should emphasize that a nephrologist-driven model for renal care will be the modus operandi. Since ESRD care is a disease management process, it is incumbent that the nephrologist be the coordinator of care for renal patients, accepting responsibility for both clinical and economic outcomes. Principal caregiver or primary care nephrologist (PCN) are terms that explain the role of the nephrologist in caring for the patient with ESRD rather than the term primary care physician (PCP). The scope of practice that should be delivered to the ESRD patient by the PCN has been developed and clearly delineates the responsibilities of the nephrologist [4]. A commitment to quality of care in a cost-effective environment will be espoused and delivery of this quality care will occur through the expertise offered by every member of the dialysis team. Appropriate information systems will facilitate the necessary communication among every member of the team (see below).

Relationships and personal connections, more than organization charts, will be the key to successful outcomes. Concepts of horizon-

tal and vertical integration will be the basis for any successful endeavor. These terms translate into a euphemism for dictated algorithms of care orchestrated by case (care) managers using all resources for comprehensive patient services that are fully coordinated and controlled by the dialysis unit team. Horizontal integration should actually be termed circular integration if viewed as the spokes of a wheel with the patient at the center of the hub (Figure 1). All systems and the personnel involved are designed to serve the patient's needs. If the design for a dialysis operation were being done by a corporation, cost may be placed at the center, profit margin being the driving force for decision-making. Later in the chapter the issue of finances will be addressed.

Performance improvement is part of the ongoing process to maximize patient care. Adapting an industrial process improvement model has been shown to achieve significant improvements in a hemodialysis (HD) program [5]. This model for improvement consists of well-defined steps for rapidly analyzing a problem and developing solutions. Typically, a department manager prepares a proposal, the proposal is then evaluated according to specific project selection criteria. Intensive implementation workshops are held to evaluate the problem and brainstorm ideas. Solutions are then implemented and the results tracked.

Key to the improvement process is an analysis of waste. This can include waste of time, idle time created when staff wait for people or machines, wasted movement of people or machines, efforts to add no value to the service received from the customer's perspective, waste of efforts spent on correction, and overstaffing.

For example, several sources of waste were identified in a hospital's HD unit [5]. The process included all members of the team, allowing them to develop the necessary solutions to problems they identified. Changes recommended by the team included the following:

- relocating the HD unit closer to the inpatient floors to cut down on patient travel time,
- reducing the floor space by nearly half to eliminate over-production waste,
- reducing supply inventory to a two-day level,
- using patient beds with scales to cut down the time needed to weigh bedridden patients,
- implementing improvements in patient transportation, and
- implementing measures that reduced the number of patients who could not complete the prescribed amount of treatment from 14% to 1%.

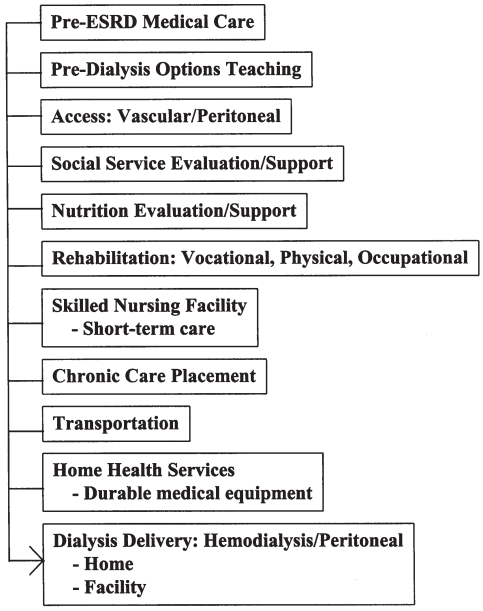

Figure 2. Vertical Integration: the continuum of service which need to be available to the patient with chronic renal failure, beginning in the pre-ESRD period and extending up to dialysis initiation and chronic treatment. Not every service will be used by all the patients.

	Dialysis Issues	
Task	How Achieved	Responsible Team Member
Dialysis Prescription	Establish goals	Nephrologist
Dialysis Delivery	Each treatment	Nursing/Technician Staff
Adequacy of Dialysis	Monthly lab review	Nephrologist
Social Service	Monthly review	Social Worker
Nutrition	Monthly lab review	Dietitian
Rehabilitation		
– Physical	Establish goals	Physical Therapist
– Occupational	Evaluation of home needs	Occupational Therapist
– Vocational	Employment status	Rehabilitation Commission
Scheduling	Written/Verbal communication	Head Nurse and Secretary
Water Treatment	Maintenance schedule	Technician
Supplies	Order schedule	Renal Administrator

Figure 3. Dialysis care team. Some of the issues which must be addressed on a regular basis. The entire team should meet monthly to review patient programs and dialysis unit issues. A core group of nephrologist, nurse, social worker, and dietitian must then sit down together with the patient on a regular basis at least 3 times/year to review goals, progress and achievements. Other members of the care team are added on an as-needed basis.

Table 1. Definitions of Practice Guidelines, Clinical Pathways and Clinical Protocols

Practice Guidelines: guide for decision making in an ambulatory care setting over time.

Clinical Pathways: procedure-based and used primarily in the in-patient setting.

Clinical Protocols: specialty-based consensus guides for management of complex/unusual diseases.

ices can potentially be done in a capitated environment (See section on Finances). Let us now examine in-depth the actual meaning of circular (horizontal) and vertical integration, as seen through the personnel involved and the functions they perform. Figure 3 outlines the dialysis issues which need to be addressed by all members of the dialysis care team.

Circular Integration

Vertical integration is all the services that should be in place to maximize delivery of patient care (Figure 2). If we are going to serve the total needs of the ESRD population, then every component of care, both in and out of the dialysis unit, should be planned in an integrated fashion. Cost-accounting the serv-

The roles that need to be fulfilled for any organization must be accompanied by detailed job descriptions for every position. The job description would serve as a benchmark against which performance is measured. Certain terms and definitions need to be explicit so all members of the team are on the same

Table 2. Medical Problems Which Need to be Addressed During the Course of Renal Failure and with ESRD

– Hypertension
– Anemia
– Metabolic acidosis
– Renal osteodystrophy
– Nutrition

wavelength. Three key definitions are given in Table 1.

Role of the Nephrologist

Physician leadership is key to an integrated delivery system survival.

Quality of care will be scientifically driven by practice guidelines, best demonstrated practice and clinical pathways. Medical care areas which need to be addressed by the nephrologist are noted (Table 2).

While clinical guidelines are considered important mechanisms to improve quality of medical care, problems with implementation may limit their effectiveness. Use of a computer-based system for clinical guidelines for patient management can improve documentation and compliance with guidelines. Percentage of time spent on individual activities can decrease while also decreasing overall cost to the system [6]. Selecting guidelines to maximize overall population benefit can compete with selecting the best guidelines for individual patients. Use of cost-effectiveness analysis is necessary to make optimal decisions [7]. There is a need to prospectively and retrospectively validate guidelines to make sure that continued use is warranted. Outcome surveillance must be part of the feedback loop in validating guidelines [8]. Simplicity leads to success with clinical guidelines, the constant focus being on quality.

The nephrologist will be responsible for adhering to performance measures mandated by the Health Care Financing Administration (HCFA) and administered through the ESRD Networks. Integrated information needs to provide data for performance measurements and resource management techniques. Dialysis Outcome Quality Initiatives (DOQI) [9, 10] will be the starting point for practice guidelines. More guidelines are to follow, the process initially being started by the Renal Physicians Association's (RPA) first-ever nephrology guideline on adequacy of hemodialysis [11].

Algorithms exist for the above DOQI practice guidelines. In addition, management schemes for renal osteodystrophy, approach to vascular access, adequacy of nutrition, and management of hypertension in the dialysis population have been developed in local markets and will expand to the national scene. Forthcoming is a guideline on who should be started on and who withdrawn from dialysis. Evidence-based medicine, adhering to principles developed by the Agency for Health Care Policy and Research, will drive the positive changes designed to improve patient outcomes [12]. "Evidence-based medicine" has potential problems since it represents collective data and pertinent sub-groups formed by such cogent clinical features as severity of illness, co-morbidity and other clinical nuances can change situations. The laudable goal of making clinical decisions based on evidence can be impaired by the restricted quality and scope of what is collected as "best available evidence". Always remember the difference between a guideline and a mandate [13].

Key points of a practice guideline need to be culled out and presented in an annotated

algorithm. Algorithms are the best way to graphically represent the detailed process physicians go through in managing a patient and it can be computerized relatively easily. The format of the guideline is really immaterial, it is the way in which it is put together that is critical, always focusing on quality and scientific evidence. All guidelines should adhere to the same process.

- An evidence-based guideline developed by a reputable source.
- The guideline is submitted for broad nephrology peer review to determine if the guideline will improve the quality of care and if the scientific evidence supporting the guideline is acceptable to physicians.
- Data are collected both to demonstrate "quality gaps" in current practice and as a measure of improvement after implementation of the guideline. One of the least effective things in a quality improvement initiative is to make the performance objectives too obscure.

Continuous quality improvement (CQI) is a necessary and critical component of practice guidelines because it encourages each provider to look at their own program and define areas for improvement, then design action plans to meet these goals. A data feedback mechanism is the link in the system to provide physicians with their performance and compare it to colleagues within the region, network, state and nation. Identifying areas that need improved service is a natural sequence. Once data is presented it is important not to micro-manage physician behavior. Micro-management is time-consuming for physicians and it does not add value to patient care. The goal of CQI is to obtain the best results and physicians will usually respond to competition (keeping up with their colleagues), as long as the data is scientifically sound. Offer physicians the tools and data they need to deliver optimal medical treatment while also assisting patients in developing self-management skills. The future of practice guidelines can be framed in their being a point-of-reference in a decentralized health care system. The 18 ESRD networks can assist a dialysis unit in its region to pinpoint and correct problems. Guidelines and outcomes data generate great discussion. So often physicians assume that their colleagues treat patients much in the same way that they do, but when an evidence-based guideline or some other outcomes data are put on the table, it turns into serious discussions about practice variances, and that is where the changes start to happen [14].

Role of the Head Nurse and Nursing Staff

The head nurse should be the advocate for the nursing staff and technicians who care for patients. Making sure staff adheres to established protocols needs to be a primary responsibility. This individual also will be an active participant in evaluating outcomes data and participate in changes in medical technology. With large national dialysis chains it is imperative that the nurse always remain the voice for his or her staff rather than be seen as the bidding horse for the corporation.

The head nurse can develop a computer-based work schedule for all staff members as well as for rounding physicians and patient schedules. This approach helps track patients in-hospital, and it serves as a reminder to make sure that there is adequate communication between hospital and dialysis facility regarding the particular patient. Schedules are updated monthly and everyone knows who is available. A color coordinated scheme will allow easy identification and facilitate planned meetings around patient care. Such

Table 3. Components of Predialysis Education Program Provided by the Nurse Educator

- Utilize videos, booklets and other teaching tools to enhance dialogue
- Education on all modalities of ESRD care:
  - Hemodialysis
  - Peritonealdialysis
  - Transplantation
    - Living related donation
    - Emotionally related donation (non-blood relation)
    - Cadaver donation
- Explanation of patient responsibilities on dialysis

schedules can be programmed under a schedules option in the computer.

A vital role for a member of the nursing staff is options teaching for all new ESRD patients. One or 2 individual nurses should be assigned the task of educating patients about their specific options with regards to HD, peritoneal dialysis (PD) (various modalities) and transplantation (if appropriate). The options education nurse will coordinate all of the care initially and help walk the patient through the various aspects of the system they will encounter when starting dialysis (Table 3). Education information for patients should be multifaceted.

- A patient handbook concerning all options allows patients to read information and assimilate that which was discussed in person. The patient retention at initial verbal discussion will be minimal because of underlying anxiety.
- An individualized patient training plan should be recorded.
- A monthly patient newsletter acts to solicit patient input into the process. It will give the patient a "buy in" to the dialysis process and help them participate in their own care. Such a newsletter should be written by both staff and patients, highlighting the positive aspects of patient education. Participation in and discussion of unit issues can be raised in a newsletter. Scientific information about the significance of lab values can be highlighted. A newsletter format will allow the patient to read information outside of dialysis unit and will this information will reinforce positive patient behavior.
- Video tapes should be available which emphasize options teaching, compliance with dialysis prescription, patient awareness about chemistries, blood pressure control, and dose of dialysis. The National Kidney Foundation has a series of educational tapes that are "user friendly" and should be used with every formal pre-dialysis teaching and training program of patients. ESRD is a family issue and no member of the family should be excluded since family members help support the patient outside of the dialysis unit. The goal of education material is to empower the patient to participate in self-care.

In chronic illness, day-to-day care responsibilities fall most heavily on patients and their families. Effective collaborative relationships with health care providers can help patients and families better handle self-care tasks. Collaborative management is care that strengthens and supports self-care in chronic illness while assuring that effective medical, preventive and health maintenance interventions take place and nursing is the natural liaison in this process.

- Collaborative definition of problems: patient-defined problems are identified along with medical problems diagnosed by physicians.

– Targeting, goal setting, and planning: patients and providers focus on specific problems, set realistic objectives, and develop an action plan for obtaining those objectives in the context of patient preferences and readiness.
– Creation of a continuum of self-management training and support services: patients having access to services that teach skills needed to carry out medical regimens, guide health behavior changes, and provide emotional support.
– Active and sustained follow-up: patients are contacted at specific intervals to monitor health status, identify complications, and re-enforce progress necessary to implement the care plan [15].

The head nurse should publish unit specific results with regards to adequacy of dialysis (as measured by *Kt/V* or urea reduction ratio). Publication of results addresses the issue of dialysis unit accountability to the patients.

The head nurse should coordinate education for every member of the staff with regards to the concept of customer service. The patient must be treated like a valuable customer and therefore every individual interacting with the patients must undergo training about customer (patient) sensitivity. We often forget that the person who answers the phone in the dialysis unit can be the most important individual in the health care chain. From the physician on down, we must all recognize the value of patients and always respect their individuality.

With the introduction of the case (care) manager into the dialysis unit, it is important to note the distinction between the nursing staff and the care manager in an integrated system. Nurses provide direct care to patients in the dialysis unit and the care manager coordinates care across all settings encountered by the patient (which requires interacting with the patient).

Role of Case Manager/Care Coordinator

The traditional role of a case manager has been an individual who works for the insurance company/HMO/Managed Care Organization (MCO), serving mainly in the role of retrospective quality assurance (which translates into “why is this patient still in the hospital?”). Case management can be defined as a collaborative process that assesses, plans, implements, coordinates, monitors, and evaluates options and services to meet an individual’s health needs. Communication and utilization of available resources help promote quality of care and cost-effective outcomes. The new case manager, more properly called the care manager, is an emerging key player responsible for attention to patient care and is an integral part of the dialysis team. This individual is accountable to the nephrologist. Patient evaluation by the care manager will occur both in the dialysis unit and at home, closing the loop that is often open. A more complete picture of the patient will result in an improved overall health care plan for the patient [16]. Understanding the psychosocial milieu of the patient will allow adaptation of an individual care plan designed to produce the best outcomes. For the patient who needs assistance/support, it is even possible for the care manager to accompany the individual to appointments outside the dialysis unit. This care manager will document improved quality outcomes and cost-effective resource utilization. The end result is that patients, health care personnel, administrators and payors are equally satisfied. Financial resources are necessary to pay these senior nurses with years of experience in dialysis and it is a worthwhile investment because of expected improved outcomes and reduced costs through coordinated and integrated patient services.

Reduced hospitalization days will be the major factor in reducing overall costs to the system. Since complications of vascular access are the most common cause for hospitalizations, monitoring the access on a prophylactic basis will hopefully decrease problems with access thrombosis, septicemia, and inadequate dialysis due to a failing fistula or graft. In addition, transportation to and from dialysis would be arranged via the cheapest means once all the issues on the patient's environment are understood. Excessive use of ambulance transportation, another major cost to the system, should decrease with detailed evaluation of the patient's total situation. Impediments to moving the patient along the entire continuum of care should be identified by the care manager, and this will allow for effective interventions to be initiated.

The ideal candidate for care management is a patient with clinically complicated diagnoses who consults multiple providers for a variety of health care decisions. Typically, this is a high-risk patient with serious co-morbidities and escalating disease. This description fits our aging dialysis patient [17]. Care management applied to ESRD is done through interaction with every member of the health care dialysis team, utilizing the resources in the facility and community to deliver the necessary patient services. Communication is a key element in the success of the renal nurse care manager, taking place during scheduled multi-disciplinary conferences, summarized information updates or specific meeting formats.

CQI tools with integrated managed systems offer a useful and effective means to process large amounts of data. Patient assessments and thorough data analysis help to identify those treatment areas that offer opportunities for greatest impact. Risk assessment can be done using the Index of the Disease Severity (IDS). This system allows patients to be characterized by the extent and severity of co-morbid conditions. Once the severity of the various co-morbid diseases are identified, the patient can be characterized into a low, medium or high risk category. Risk adjustment is essential before comparing patient outcomes across dialysis facilities. Several different severity measures are in place and it is critical to have a single measurement that best defines the dialysis population. At this time there is no single severity measure that has been defined and utilized for the ESRD population [17]. Managed care is outcomes-driven and the care manager is the necessary step that allows facilities to drive the best outcomes.

The Role of the Rehabilitation Specialist

There are 3 major components of rehabilitation: vocational, physical, and occupational. The goal is to maintain the patient in a healthy and productive state. Keep the patient in the workplace if at all possible, if that was the situation in the pre-ESRD period. Expert medical management, best delivered by the nephrologist in the role of principal care giver, provides the best chance for maintaining a healthy patient while chronic renal failure progresses toward the inevitable ESRD. Vocational rehabilitation should be started on a prophylactic basis, determining the needs for adaptation in the workplace to accommodate the patient's failing health and desire to remain productive. A liaison with the state/county/local rehabilitation commission should be part of the organizational/administrational design for the dialysis unit. Developing model programs that can be simulated in other regions is a way of serving the needs for all chronic renal failure patients.

Maintaining the patient in the workplace throughout the transition from progressive renal failure to ESRD has been shown to be cost-beneficial. A working patient has a better self image and fewer physical problems. The Life Options Rehabilitation Advisory Council (LORAC) has examples of model programs that facilitate the stated goal of workplace productivity [18]. For example, a temporary employment agency offered dialysis patients an introductory course on temporary secretarial work. For every 3 months the patients stayed employed at the temporary agency they were offered an additional training period to enhance their skills. Therefore, they became more valued employees (translated into a higher level of pay). Every 3 months the cycle continued, the patients learning greater degrees of computer skills and therefore becoming more highly valued workers. Permanent employment was the end result for a large percentage of the patients who initially entered the program, the work schedule adapted to the dialysis routine.

A program can only work if there is up-front attention paid to insurance issues. The patient cannot be penalized for accepting part-time or full-time employment while on dialysis if work proves to be an economic detriment. Innovative ways need to be created to prevent the working patient from losing health coverage/insurance benefits.

Physical therapy/rehabilitation should also be employed as a prophylactic measure. A detailed exercise program should be started for each individual as they progress towards ESRD. Keeping patients active and physically fit before dialysis is likely to enhance the quality of life once on dialysis. It is equally important for the patient on dialysis to continue to exercise. Exemplary rehabilitation practices have been established in a number of dialysis units and LORAC can provide a list of facilities that have received awards for their rehabilitation programs [19]. Exercising on dialysis achieves a greater degree of compliance with the designed program as compared to the patient attempting exercise at home as the initial step. Once the patient incorporates exercise as a routine matter, then a program of fitness can be continued at home. However, designing a program for home use at the outset if doomed to failure.

Renal rehabilitation is the process of helping dialysis patients resume productive activities, including independent living. As conceived by LORAC, the core principles of renal rehabilitation are the “five E’s; Encouragement, Education, Exercise, Employment, and Evaluation” [20]. Using the five E’s as the basic principles will help incorporate rehabilitation into the daily activities of a dialysis facility. Several issues should be addressed when starting a renal rehabilitation program. The following must be done to get started:

- establish pre-requisites for renal rehabilitation before the program starts,
- provide adequate dialysis,
- maintain good nutrition,
- manage anemia,
- maintain vascular access,
- build staff commitment,
- plan a rehabilitation program,
- identify a rehabilitation champion,
- designate a rehabilitation team,
- develop mission statement and goals,
- develop a program,
- identify renal rehabilitation resources,
- establish a facility baseline,
- assess facility resources,
- review staffing patterns,
- assess financial resources,
- identify potential sites,
- involve patients in your program,
- assess current patient rehabilitation status,
- discuss options with patient and family,
- match patients to appropriate programs,

– coordinate rehabilitation activities with patient schedules,
– evaluate your program,
– determine patient rehabilitation outcomes and satisfaction,
– measure staff satisfaction,
– modify your program as needed,
– collect success stories.

Following the above schemata will provide a template for moving forward [21]. LORAC has introduced the Unit Self Assessment Tool for Renal Rehabilitation (USAT) to help dialysis facilities assess their own renal rehabilitation programming [22]. USAT outlines basic, intermediate and advanced characteristics of good renal rehabilitation programs for each of the designated "five E's". Facilities can assess their programs by using this tool.

– Units without formal renal rehabilitation can use it as a checklist to identify programs that are serving rehabilitation functions.
– Facilities can select new ideas/strategies to implement.
– Units with problem areas can use it for suggestive solutions.
– It can be used as part of a CQI initiative, or to improve staff motivation.

Role of the Social Worker

A continuum of participation begins in the pre-ESRD period. The social worker will be an integral part of the patient's care team from the very beginning, identifying the psychological needs of the patient and assisting in financial adaptation to dialysis. Every attempt will be made to have the patient remain in the workforce if that was the situation in the pre-ESRD period. Once the patient stops work it is very difficult to get that individual back into the workforce. Assisting the patient to participate with self-help groups will lead to a better informed patient. Examples of effective patient self-help groups include the National Kidney Foundation, the Polycystic Kidney Research Foundation, the Lupus and Scleroderma Foundation, the Kidney Transplant/Dialysis Association (Boston area), and the American Association of Kidney Patients (AAKP).

Discharge planning can be viewed in a broad sense and the social worker is best equipped to approach this issue. Whether it be transferring the patient from the hospital to rehabilitation facility or arranging for home health aide, the social worker can utilize the resources in the community to impact on the overall care delivery system. Discharge planning involves determination of resources necessary for the patient's continued care during the course of illness, with the provision of assistance and guidance for these services. Home health care authorization and arrangement for ancillary services at home is part of the services. This critical piece of patient services contributes greatly to the quality of care and the social worker will assure the most appropriate services be utilized in accordance with best practice methodology. See Table 4 for a summary of social worker responsibilities when dealing with ESRD patients.

Role of the Renal Administrator

The administrative functions of the dialysis unit rests in this individual's hands. This person will coordinate the care delivered by the physicians, nurses, technicians and support staff. Besides the obvious administrative issues, the renal administrator should keep abreast of all legislative issues. Interpretation of the significance of these issues needs to be shared with all the staff because it impacts on

Table 4. Some of the Social Worker Responsibilities in the ESRD Setting

– Support network for patient
family
self-help organizations
– Finances
insurance pitfalls
implications of remaining in the workplace regarding insurance coverage
– Transportation
parking vouchers
cab
chair car
ambulance
– Counseling
is there a need for short-term or long-term counseling?
– Placement
short-term rehabililtation
long-term nursing home/assisted living

the functioning of the dialysis unit. As part of a large dialysis chain, the renal administrator needs to coordinate the interaction between the corporate and the facility quality assurance committee.

Water Safety

Guaranteeing safe water is a critical issue that is often delegated to technicians, sometimes with a little oversight. Water needs to be safe and an effective purification system for HD must be in place because of potential life-threatening adverse effects. HD water purification guidelines have been established by the American Association of Medical Instrumentation (AAMI) [23]. Guidelines for water safety have been published by the Office of Device Evaluation, Center for Devices and Radiological Health, of the Food and Drug Administration (FDA) in the publication "Guidance for the Content of Pre-Market Notifications for Water Purification Components and Systems for Hemodialysis" [24]. The FDA recommends that pre-market notifications include:

- the name of the device, including trade/proprietary name as well as classification (i.e. water purification system for HD);
- a list of the establishment registration number, if applicable, and the owner/operator submitting the pre-market notification form;
- the generic class (Class II) and the panel (78 Gastroenterology/Urology);
- safety and effectiveness information (required by the Safe Medical Devices Act of 1990);
- copies of proposed labels and advertisements describing the component/system, its intended use and directions for use; and
- a comparison of the component or system to a legally marketed predicate device.

HD water purification issues should include reverse osmosis, deionization, water softness, carbon filtration tanks, sediment and cartridge filter, ultrafilters, ultraviolet disinfection units, and water storage tanks. The FDA has stressed the importance of safe and effective water purification systems for HD. Adverselly effects of inadequate or malfunctioning purification equipment include nausea, vomiting, anemia, hemolysis, metabolic acidosis, bone disease, neurological deterioration, pyrogenic reactions, and death. Addressing all of these issues needs to be under the responsibility of the renal administrator. The actual controlling and monitoring of the water treatment equipment to improve dialysis patient outcomes should be part of the job description for the

technician assigned this responsibility [25]. Problems related to water safety have been the cause for several law suits with large settlements to injured patients or their families (in cases of death).

Administrators must include all members of the patient care staff in the implementation of the DOQI guidelines. The skills in data collection, analysis, and intervention that the clinical and technical staff learn and practice because of the DOQI guidelines will improve clinical outcomes and prepare them to transfer those skills to other ESRD problem areas [26].

Patient

The patient is the center of the wheel and all the spokes of the health care team relate and connect to this individual. Patient rights and responsibilities must be defined. The American Association of Kidney Patients has adopted a statement of patient rights and responsibilities from ESRD network #15 [27]. Such a statement is an important part of a patient's care, the expectation being that observance of such a statement will contribute to more effective care and greater satisfaction for both patients and staff. Every patient has the right to be treated with respect, dignity and consideration of his or her rights as an individual by everyone involved in their care. Privacy and confidentiality are critical during case discussions, consultation, examination and treatment. All communications and records about patient care are to be treated as confidential, the patient retaining the right to approve or refuse release of records to any individual outside of the facility, except if there is transfer to another health care institution, or is required by federal, state, or local laws. It is the responsibility of the patient to treat the staff with the same respect and individual consideration as the patient expects for him- or herself. Honesty and directness about everything that relates to the patient's care must be forthcoming from the patient. A guiding principle, starting in the pre-ESRD era and continuing throughout the dialysis experience, is that the patient must be aware of all the options that are medically appropriate for them. Discussions about transplantation with a patient who is not an obvious transplant candidate should not be undertaken. At all times patients should understand the medications they are taking, the purposes for such and potential side effects. Pamphlets should be distributed to patients in their primary language (if possible) after an educational session so the process of education can be reinforced at home. In addition, patients should have a clear understanding of their dietary prescription.

"Advance directives" should be part of every facility's patient care plan since these directives protect the patient's rights to refuse or limit future medical treatment if the individual becomes unable to communicate their wishes. The concepts of living wills and medical durable power of attorney should be presented to patients.

Once dialysis starts, the patient should be informed about the dialysis prescription and desired goals of treatment. Clearance methods should be briefly explained and the particular method used by the dialysis unit to measure adequacy of dialysis needs to be noted. Patient expectations for compliance with their dialysis prescription (showing up on time and staying for the prescribed duration of treatment), taking prescribed medications, and following the dietary prescription should be part of a described agreement. If patient proves to be non-compliant with any aspect of their regimen, a written contract should be drawn and the patient made to understand the seriousness of their behavior. Repeated non-compliance

should result in the patient being told they should seek another dialysis program or begin home HD/PD. If transfer to another facility is necessary, it is the patient's responsibility to secure the services of a nephrologist to provide medical management at that new facility. Patients should be told that it is unfair to ask members of the health care team to participate in inadequate care. Why should the team do more for the patient than that individual is doing for him- or herself?

Integrated information systems that provides data for performance measurements and resource management are critical for any facility to function effectively in the context of circular integration. The goal is to turn data into information for effective disease management. Such an information system should facilitate patient management, create a seamless coordination of benefits, and support health maintenance from office to dialysis unit to hospital to home. With so many personnel involved in the care of the ESRD patient, there is a critical need for information to be readily available to maximize patient care. Patient confidentiality would be protected by the "need to know" principle. The computer logon code would provide only the information that is pertinent for the particular member of the health care team to deliver services.

Users of the health care system (consumers) must have their perspectives incorporated into any measure of quality. It is important to know the patient's perspective of the "definition of quality". Patient satisfaction is not always equated with quality since amenities (e.g., food, parking, cleanliness) are frequently confused by the patient as measures of quality when they actually reflect satisfaction. Satisfaction implies only that expectations have been met. Patients can be satisfied with care that is not high quality and they can be dissatisfied with quality care [28]. The Kidney Disease Quality Of Life (KDQOL) questionnaire has been shown to be an effective tool in measuring quality as viewed from a patient's perspective. Methods need to be developed for dialysis patients that adequately reflect quality in terms they can understand. Summary evaluations need to be an immediate goal so patients can be further empowered to be active participants with their care on dialysis. It is always critical to remember that patient satisfaction is most correlated with an individual's ability to choose their personal physician in an HMO [29]. Patients who are assigned physicians in dialysis units for coverage purposes can be dissatisfied at the outset. Patients satisfaction can also be related to public release of consumer reports. If patients know other individuals are satisfied with their care it may assist patients in making informed health care choices. This approach can also facilitate improvement in quality of care because of competitive marketplace forces [30].

Workforce

Given the increasing oversupply of physicians, the American College of Physicians recommends that no new medical schools be created, that total enrollment in the United States medical schools not increase, and that the number of international medical graduates entering residency training in the United States be restricted [31]. Since the number of first-year residents will likely be linked more closely to the annual number of medical graduates in the United States, Medicare payments for medical education and training will be made only to HMO's that actually incur education and training costs.

Changes in the direction of internal medicine training will impact nephrology (as well as every other medical subspecialty). The bottom line is that there will not be an increase in

the number of nephrologists trained over the next decade. Therefore, in order to meet the needs of the ESRD population, our delivery system of care will have to change. There will be too few nephrologists to deliver care to the growing dialysis/transplant population as viewed from a 1990's perspective. Use of alternative caregivers will be employed to a greater extent than ever before, especially the number of health service coordinators/case managers/care managers will increase. Physicians will delegate day-to-day management issues to other members of the health care team, the nephrologists focusing on the major medical problems that reflect his or her expertise. Such coordination of care will only be effective if a communications system is operational. This will require a commitment for all individuals to utilize a computer communication system so that there are no gaps in patient care as a result of inadequate communication. Those physicians who do not become computer literate will find their roles delegated to other individuals who know how to effectively communicate.

Issues related to workforce evaluation and needs for nephrology up to the year 2010 have been addressed by the Workforce Needs in Nephrology Task Force [32]. The combined efforts of the American Society of Nephrology, American Society of Pediatric Nephrology, American Society of Transplant Physicians, National Kidney Foundation and Renal Physicians Association produced a study that provides various scenarios estimating annual needs for nephrology trainees through 2010. Graduated projections for nephrology trainees are based on the rate of growth of patients with ESRD, physician full-time equivalent (FTE) needs for renal patient care, and ESRD mortality rates relative to current levels. The Task Force report is worthwhile reading because it views future training needs for nephrology, recognizing that the state of medical care, biomedical research and academic medicine are in astonishing flux. The issue of Foreign Medical Graduates (FMGs) and their impact on nephrology, especially in light of changing legislation, is noted in detail.

Finances

Financial management of the entire dialysis process requires expertise that evades most nephrologists. There is the need to find expert help to define cost parameters, track funds management and assist with contract negotiation. All of the large dialysis chains have financial departments in place. However, there are several areas that should be understood by the nephrologist, the major question being what is the cost effectiveness of test- and treatment strategies [33]. In the present era of cost-containment, physicians need reliable data about specific interventions. How to interpret economic analyses and estimate their own costs of implementing recommended interventions is a necessary learning step for the nephrologists.

Statements regarding cost without substantiating data are made habitually in reports from dialysis units, especially in the hospital setting. Data on expenditures, start-up costs, and general overhead are frequently neglected in looking at the bottom line. There is a need for cost data in a standardized protocol so that missing data can be detected. A bridge between care delivery and economic analyses is a necessary link [34].

The market is now headed by 3 vertically integrated mega-providers. Fresenius Medical Care (FMC), Gambro Healthcare, and Total Renal Care (TRC) provide dialysis for more than half the United States ESRD population. A number of other organizations are growing and are definitely large-scale provid-

ers (e.g. Renal Care Group), with further consolidation on the near horizon. Large national chains have definitely changed the delivery of care. Data management has improved, but doctor-patient interaction has suffered. In many cases, the doctor-patient relationship has become a nurse-patient or staff-patient relationship, reflecting a decrease in physician presence in the dialysis unit. The patient has often become a pawn in the "return on investment" game that results from the selling of individually-owned dialysis units to one of the national companies [35].

The publicized rationale for consolidation is to obtain economies of scale (i.e. reduce administrative overhead by eliminating duplication). Over the past 2 decades the dialysis landscape has changed dramatically, related in part to increasing regulation as a consequence of government experiences with escalating costs beyond the anticipated projections. Declines in reimbursement have led medical entrepreneurs to seek individuals skilled in business management to help run their medical operations. Cost control as a major issue has occurred as a result of the composite rate payment schedule for dialysis. Larger organizations negotiate better pricing for supplies. In vertically-integrated organizations, much of the equipment and disposables will be supplied internally. This internal supply line apparently represents significant savings since the marketing and distribution costs can be virtually eliminated. At times the focus on the patient can be lost in economic wranglings.

Financial compensation for nephrologists is rapidly changing. The old days of fee-for-service in an unfettered manner is over. Capitation can be employed as a method of payment that encourages routine care and a modified fee-for-service may be utilized for circumstances defined as extraordinary [34]. A new approach for reimbursement could be the single specialty (nephrology) carveout from a payor [36]. Advantages of such a carveout system include:

- the payor's ability to transfer risk to the physician group,
- the ease of negotiating a single-specialty carveout with the payor than a global capitation contract (for all services to be delivered),
- a possible increase in practice volume and thus physician income (assuming that the reimbursement is adequate),
- participating single-specialty independent practice associations' (IPAs) exclusive contracts with the payor,
- forcing the physician to closely observe his/her practice efficiency,
- a long-term relationship between physician and payor if your physician group is the first in the market and your group's performance has become known to the payors, and
- negotiation of a contract with multi-specialty IPAs, which can get access to more of the premium dollar because of a demonstrated track record with payors.

There must be detailed explanations of how bonuses will be allocated among the physician group. In a managed-care capitated environment, physicians should be eligible for incentive pay based on improved outcomes, open access to care and patient satisfaction results [34]. Reimbursement incentives should never be tied to cost savings generated by denial of services.

An information booklet must be maintained in a dialysis unit that details issues of financial concern involving the patient [37]. Evaluation and management services expected as part of the monthly capitation payment (MCP) should be a clear statement for patients to understand. This is a critical reminder to physicians of their responsibilities to the patient.

For physicians themselves there must be a similar booklet that notes the required documentation for every level of service. Physicians need to know how billing is done within Medicare regulations. This booklet will need to be updated because of the rapid changes that are occurring in the area of reimbursement. The steady shift of all segments of the population from a fee-for-service to a capitated environment mandates constant physician updating.

There is a demonstrated need to avoid unnecessary test-treatments when viewed in the context of quality adjusted life year (QALY) [38]. Physicians will need to understand the issues of sensitivity analysis when viewing such QALY, which relates to the value of a specific strategy (test or treatment) as viewed by the general public (e.g. how much should society pay for an intervention when considering the benefit to the patient and society?).

Optional dialysis treatment requires an informed patient, a dedicated staff, modern equipment and computer facilities that will provide relevant information.

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Management of Poisoning and Drug Overdose

Nuhad Ismail, Roxana Neyra and Salim Mujais

Most poisonings with common intoxicants are effectively treated with only supportive measures [1 – 3]. This includes appropriate therapy for the complications that often accompany intoxications, namely hypotension, arrhythmias, and seizures. Antidotes are also available for many intoxications (Table 1). They work by directly binding the toxin (e.g. digoxin-specific F_{ab} fragents), by altering its metabolism (e.g. N-acetylcysteine in acetaminophen overdose), or by reversing its toxic effect (e.g. naloxone in opiate intoxication).

Initial Management

The foremost priorities in any intoxication are:

- establishing an airway,
- providing ventilation, and
- maintaining adequate circulation.

Subsequent management should include intravenous (IV) glucose for possible hypoglycemia in any patient with coma or seizures, naloxone to reverse narcotic-induced respiratory and central nervous system (CNS) depression, and oxygen (O_2). Thiamine also should be administered to any patient with altered mental status to prevent or treat possible Wernicke's encephalopathy [1].

The next step in the care of any patient with presumed drug toxicity is the administration of activated charcoal. Routine gastric emptying procedures should be discouraged given their serious morbidity, and only considered in conscious patients who have ingested non-caustic substances not adsorbed by charcoal (iron, lithium, methanol, ethylene glycol, boric acid, malathion) [1, 2].

Multiple doses of activated charcoal (MDAC) prevent poison absorption and increase poison clearance through intestinal dialysis [4, 5]. Recommended initial adult dose is 50 – 100 g in 250 mL water, then 30 g every 3 – 4 hours. It should be mixed with a cathartic (70% sorbitol is most effective). Shorter dosing intervals should be used for drugs with short half-lives $t_{1/2}$ (theophylline) and longer intervals for drugs with longer $t_{1/2}$ (phenobarbital). Whole bowel irrigation with a polyethylene glycol-electrolyte solution may also play a role in the future for treating acute overdose [6]. This technique has been useful in iron poisoning, lithium toxicity, and in cases of ingestion of cocaine packets or "crack" vials.

Forced diuresis and the manipulation urinary pH can abet the excretion of certain toxins [7]. An alkaline diuresis (urine pH 7.5 – 8.0), achieved by infusing 5% glucose in water (D_5W) with 2 ampules of sodium bicarbonate ($NaHCO_3$) at 250 mL/hour, can hasten the renal excretion of salicylates and long-acting barbiturates. Urinary acidification (urine

Table 1. Antidotes for Selected Poisonings

Poison	Antidote	Adult dose and comments
Methanol/ethylene glycol	Ethanol	Loading: 0.6 g/kg or 10 mL of 10% solution/kg PO, NG, or IV Maintenance: 154 mg/kg/hour (alcoholic) 66 mg/kg/hour (non-alcoholic) Double dose during hemodialysis Titrate to blood ethanol level + 100 mg/dL (22 mmol/L)
	4-Methyl pyrazole*	Limited experience Loading Dose = 15 mg/kg IV followed by 10 mg/kg IV every 12 hours for 48 hours then 15 mg/kg every 12 hours until ethylene glycol level is < 20 mg/dL
Digitalis glycosides	Digoxin-specific F_{ab} antibody fragents	mg digoxin ingested/0.6 = # of vials required 10 – 20 vials IV if unknown amount ingested or $\frac{\text{Serum digoxin level (ng/mL)} \times 5.6 \times \text{Wt (kg)}}{600}$ = # of vials IV
Acetaminophen	N-acetylcysteine	140 mg/kg PO, NG, or OG initially, then 70 mg/kg × 17doses
Opiates	Naloxone	usual dose 2 mg IV > 2 mg for pentazocine, butorphanol, or propoxyphene Addicts - 0.2 – 0.4 mg
Organophosphates	Atropine/ pralidoxime	2 mg atropine IV; repeat until drying of pulmonary secretions; pralidoxime 1 g IV
Tricyclic antidepressants	Bicarbonate	For cardiac arrhythmias 1 – 2 mEq/kg
Benzodiazepines	Flumazenil	0.2 → 0.3 → 0.5 mg every 30 seconds (1st three) then 0.5 mg IV every one min - total 3 mg. Not to give if coingestion of tricyclic antidepressants
Anticholinergic agents	Physostigmine	1 – 2 mg IV over 5 min only for severe delirium arrhythmias/seizures
Beta-blockers	Glucagon	5 – 10 mg IV starting dose. Titrate to response. Maintenance dose 2 – 10 mg/hour
Calcium-channel blockers	Calcium	1 g $CaCl_2$ over 5 min IV; may be repeated. Monitor serum Ca after 3rd dose
Cyanide	Lilly Cyanide Antidote Kit	Amyl nitrite vials for inhalation 3% sodium nitrite IV, 2.5 – 5 mL/min (up to total 15 mL) 25% sodium thiosulfate, 25 – 50 mL slow IV
Carbon monoxide	Oxygen	100% or hyperbaric
Iron	Deferoxamine	50 – 100 mg IV every 4 – 8 hours

PO = orally, IV = intravenous, NG = nasogastric tube, OG = orogastric tube, *Dilute in 100 mL of NS or D5W and infuse over 30 minutes.

pH 5.5) and large urine volumes are important for the treatment of amphetamine and phencyclidine (PCP) overdoses. This can be initiated by the rapid infusion of 5% glucose in normal saline (D_5NS) at the rate of 1 L every 1 – 2 hours) with arginine or lysine hydrochloride (10 g IV over 30 min). Thereafter, D_5NS is continued with either oral (PO) ammonium chloride (1 – 2 g every 4 hours) or ascorbic acid (1 g every 6 hours). Acidification of the urine is contraindicated if myoglobinuria is a concern with PCP.

Although no fatalities have been recorded, the use of forced diuresis may be complicated by the development of hyponatremia and water intoxication, pulmonary edema, cerebral edema, hypokalemia, and either alkalemia or acidemia secondary to the use of alkaline or acidic agents, respectively, in promoting the diuresis. Severe hypokalemia is particularly prone to complicate forced diuresis during alkalinization of the urine with $NaHCO_3$ and/or use of acetazolamide. The increased urine flow as well as the bicarbonate diuresis favor distal nephron potassium secretion. For these reasons, any commitment to the use of forced diuresis must be accompanied by close vigilance and measurement of urinary pH and serum electrolytes (particularly potassium (K^+)) every 1 – 2 hours initially and frequently thereafter. Hypokalemia should be corrected without delay.

Extracorporeal Techniques

Extracorporeal modalities are beneficial for many drug intoxications which are already severe at the time of presentation or refractory to the aforementioned measures [8]. The indications and benefits of these techniques are reviewed in the section dealing with specific intoxications. Toxins with a small volume of distribution (V_d), low molecular weight (MW), and little protein binding are ideally removed by hemodialysis (HD). These include methanol, ethylene glycol, isopropanol, lithium, and salicylates. Peritoneal dialysis (PD) can also remove many of the drugs eliminated by HD and hemoperfusion (HP); but, at most, it is only 25% as efficient as HD for this task. Drugs with larger MW and high protein binding and relatively low V_d, as well as lipid-soluble drugs, are best removed by HP (e.g. theophylline, phenobarbital). Drugs with large V_d and/or tight tissue binding usually are not removed well by either HD or HP. Continuous extracorporealed techniques such as arteriovenous hemofiltration (HF) or venovenous HF may be beneficial in intoxications with drugs having large V_d, extensive tissue binding, or slow intercompartmental transfer (e.g. procainamide) [9]. Unfortunately, only limited data are available for drug removal by these techniques. The pharmacokinetic properties of drugs commonly removed by extracorporeal techniques are summarized in Table 2.

Indications

HD or HP should be considered when the clinical conditions listed in Table 3 apply. These extracorporeal techniques can also be considered if the serum levels of a drug or poison are found to be increased to values known to be associated with death or serious tissue damage. Critical serum concentrations for several drugs are listed in Table 3. These are only guidelines, and the decision to institute HD or HP must be made on an individual basis.

Table 2. Pharmacologic Toxicity of Drugs that are Substantially Removed by Extracorporeal Techniques

Intoxicant	MW	Protein Binding (%)	V_d (L/kg)	Severe toxic Levels[a]
Isopropyl alcohol	60	–	0.6	400 mg/dL
Methyl alcohol	32	–	0.6	50 mg/dL
Ethylene glycol	46	–	0.6	21 mg/dL[b]
Salicylate	138	50 – 90[c]	0.2	800 µg/mL (80 mg/dL)
Lithium carbonate	74	–	0.8	2.5 mEq/L
Theophylline	180	53 – 65	0.5	60 µg/mL (60 mg/L)

[a]levels that are often lethal unless aggressively treated, [b]practically any positive level accompanied by symptoms and especially by metabolic acidosis is potentially lethal, [c]protein binding high at low (therapeutic) plasma levels and progressively lower at toxic levels

Table 3. Clinical Considerations and Drug Concentration Criteria for Hemoperfusion or Hemodialysis in Poisoning

(A) *Clinical Criteria:*
- Continued deterioration despite intensive care
- Severe poisoning with mid-brain dysfunction
- Appearance of complications of coma
- Impairment of normal drug excretion (e.g. ethchlorvynol overdose in a cirrhotic patient)
- Poisons with metabolic and/or delayed effects (e.g.paraquat and phalloidin)
- Poisoning with an extractable drug removed at a greater rate than endogenous elimination

(B) *Biochemical Criteria:*
A potentially lethal amount has been ingested: phenobarbital (10 mg/dL), other barbiturates (50 mg/dL) glutethimide (4 mg/dL), ethchlorvynol (10 mg/dL), meprobamate (10 mg/dL), paraquat (0.2 mg/mL).

Hemoperfusion (HP)

HP is a process whereby blood is passed through a cartridge packed with a sorbent (activated charcoal or carbon). Two other sorbents may be used: ion exchange resins and non-ionic macroporous resins. The commonly used HP devices (Table 4) contain 70 – 300 g of activated charcoal, coated with polymer membranes ranging in thickness from 0.05 – 0.5 µm. Maximal adsorptive capacity is achieved through high surface porosity and high surface area (SA; approximately 1000 m^2/g). Each manufacturer produces cartridges with different amount of sorbent and different coating material. The Clark (company, etc.) cartridges are unsterilized (longer shelf life) and must be steam autoclaved prior to use. Gambro cartridges are sterilized with ethylene oxide. Erika cartridges are sold gamma sterilized and require no further sterilization. Clark cartridges are claimed to have less incidence of clotting because of the heparin hydrogel coating.

Table 4. Characteristics of Some Available Hemoperfusion Devices

Manufacturer	Device	Sorbent	Coating	Coating thickness	Grams of charcoal-carbon	Adsorbent surface (m^2)	Sterilization by manufacturer
Erika	Hemocart Alukart	Carbon	Cellulose Nitrate	< 0.05 μ	65, 80, 155	65,000, 200,000 104,000	Gamma Irradiation
Gambro	Adsorba 300 C	Charcoal	Cellulose	3 – 5 μ	150, 300	300,000	Ethylene Oxide
Clark Research and Development	Biocompatible Hemoperfusion Systems	Petroleum-derived carbon	Heparin-hydrogel	–	50, 100, 250		None

HP circuitry (Figure 1) is similar to HD arrangement, except that no blood warming apparatus is necessary unless the patient is hypothermic. Heparin requirements are slightly higher than HD (approximately 6000 U/session) because the charcoal adsorbs some of the heparin. Heparin should be given in amounts sufficient to maintain the activated clotting time (ACT) or whole blood partial thromboplastin time at about twice the normal value. The most efficient removal of toxin is achieved with blood flow rates of approximately 300 mL/min, and the most appropriate temporary vascular access to enable efficient treatment of poisoning is percutaneous cannulation of the femoral, internal jugular, or subclavian veins.

Priming the HP Circuit

Setup and priming procedures differ somewhat depending on the brand of cartridge used, and the manufacturer's literature should be consulted in all instances. The HP cartridge must be primed in a vertical position with the arterial side facing down. One manufacturer (Gambro) recommends that its cartridges be rinsed initially with 500 mL of D_5W to load the charcoal with glucose. This maneuver is alleged to result in a lesser drop in the serum glucose level during the HP treatment. Other manufacturers do not recommend a glucose rinse.

After the glucose rinse (if one is used), the cartridge is rinsed with 2 L of heparinized (2500 U/L) 0.9% sodium chloride (normal saline, NS) solution at a flow rate of 50 – 150 mL/min. In rinsing Clark cartridges, the manufacturer recommends that the final liter of rinsing fluid be infused at a relatively rapid rate, i.e. about 150% of the anticipated blood flow rate through the device (e.g. 300 mL/min if the blood flow rate will be 200 mL/min).

Pharmacokinetic Principles of HP

By measuring the concentration of a given drug in the blood just before the blood enters

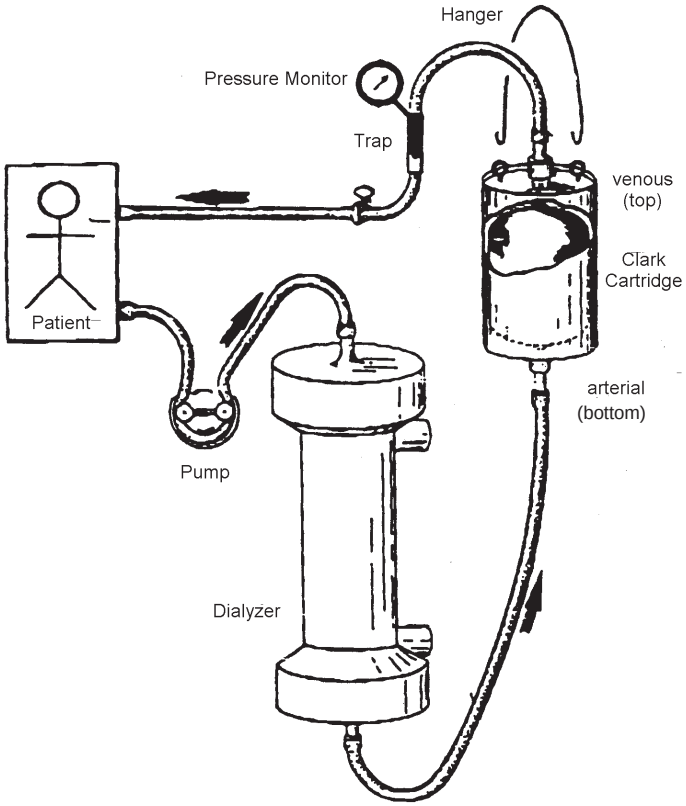

Figure 1. Schematic of a HP circuit. The Clark Biocompatible HP System may be used in conjunction with, or without, hemodialysis. Arrows indicate flow direction. (Clark Research and Development, Inc. Number 13 Park Lane, Folsom, Louisiana 70437)

and as it exits the HP cartridge, one can easily calculate the extraction ratio (ER) Of the drug with the formula: ER = (A-V)/A where, A = Concentration of toxin at inlet to HP cartridge, and V = Concentration of toxin at outlet; a ratio of 1.0 signifies complete extraction of the drug in one pass. By knowing the concurrent plasma flow rate through the cartridge, one can calculate the clearance rate (clearance = ER × Q_B, where Q_B = blood flow rate, in mL/min).

Data on drug ERs suggest that charcoal hemoperfusion is efficient in extracting a wide variety of poisons from the circulating blood, including theophylline (ER = 0.7), ethchlorvynol (ER = 0.7), methaqualone (ER = 0.5 – 1.0), phenobarbital (ER = 0.5) and glutethimide (ER = 0.65), as well as paraquat. However, despite the very high ERs and clearance rates that can be obtained with HP, other theoretical and clinical factors must be taken into consideration when assessing effectiveness of HP in the therapy of intoxications. These theoretical considerations focus on the fact that many common intoxicants have pharmacokinetic properties which predict that cleansing of the circulating blood, no matter how effectively done, may not result in a clinically detectable beneficial effect. These considerations also reveal that evidence derived only from ERs and clearance data can be misleading. After absorption, the distribution of each drug in the various body compartments is highly individualized and depends on several factors, which include the MW of the drug, its ionization at the prevailing pH of body fluids, its lipid solubility, the degree of protein binding, and the apparent volume of

distribution (V_d). The interplay of these factors determines not only the total amount of the drug that is present in various body tissues and in the extracellular fluid and plasma, but also dictates how easily the drug moves from one to another compartment, and how accessible it is to extracorporeal therapy.

Importance of Volume of Distribution (V_d)

The V_d of a substance is pharmacokinetically defined as:

$V_d = X/C_P$,

where X = dose administered in mg/kg, and C_P = Serum concentration in mg/L.The V_d of a substance is the space that represents the quantity of water in which a known amount of drug would have to be diluted to yield the serum concentration. By viewing the body as one compartment in which the substance is homogeneously distributed, V_d relates the dose of drug administered to its plasma concentration by the above equation. However, most substances are not homogeneously distributed but rather vary in their concentration throughout the body as a result of lipid solubility, protein binding, active transport and pH gradients. The apparent V_d corresponds to a physiologic space only for a substance, like methanol, that distributes in body water without significant binding to tissue or plasma proteins and without significant accumulation in adipose tissue. In this case V_d = 0.6 L/kg, the equivalent of body water. A V_d greater than the actual body water reflects a high degree of tissue concentration.

V_d is clinically important in 2 ways:

– Knowing the V_d and C_p of a particular drug allows calculation of the amount of drug ingested.

– V_d is one of the factors that determines accessibility of a drug to removal by extracorporeal therapy. Large V_d implies that the drug is concentrated in less accessible extravascular compartment, and hence not efficiently removed by HP (e.g. V_d of digoxin and tricyclic antidepressants, are 6 L/kg and 20 L/kg, respectively).

Conversely, a low V_d by no means ensures success with HP. For example, paraquat, glutethimide, and short-acting barbiturates are not readily removed by HP due to tight tissue binding.

Duration of HP

Assuming first-order kinetics and instantaneous equilibration of compartments, the removal of a substance during HP follows an exponential relationship:

$$C_{final} = C_{initial}\left(e\frac{-Kt}{V}\right)$$

Where
K = clearance which is equal to ($Q_B \times$ ER), in mL/min,
t = time elapsed (mins),
V_d = volume distribution (mL),
ER = extraction ratio, and
Q_B = blood flow rate, in mL/min.

Knowing the C_{initial} and desired C_{final}, one can estimate the duration of HP required to achieve the target concentrations of the toxin or drug being removed. In practice, however, a single 3 hour treatment will substantially lower the blood levels of most poisons for which HP is effective and prolonged HP (beyond 3 hours) is usually unnecessary. Indeed, more prolonged use of a HP cartridge is inefficient, because the charcoal tends to become saturated with the toxin or drug (especially

when cartridges containing < 150 g charcoal are used). Usually, replacement of saturated devices with fresh devices is not required, and any rebound in plasma drug concentrations consequent to tissue release can be treated with a second HP session.

Complications

The principal side effect of HP with charcoal or resin preparations is platelet depletion. Most studies of HP in humans show an average loss of 30% of platelets with coated or uncoated charcoal or resin preparations [10]. Occasionally, however, a higher drop in platelet count can occur, which may give rise to clinical bleeding problems. Other side effects noted are reductions in serum Ca and glucose and transient falls in white blood cell (WBC) counts, all of which are usually mild and can be managed clinically. In addition, with the recirculation of blood in the extracorporeal circuit, there is also a mild reduction of 1 – 2°C in body temperature, and frequent body temperatures should be taken in deeply comatose patients. Although hypotension as a consequence of circulation of blood in the extracorporeal circuit is an infrequent phenomenon in drug overdosage, pressor agents like dopamine for hypotensive comatose patients should be administered distal to the sorbent devices, since they are also adsorbed by the sorbent preparations. The observed falls in platelet concentrations usually return to normal limits within 24 – 48 hours following a single HP.

Intoxications Which Respond Readily to Extracorporeal Therapies

Intoxications with Methanol, Ethylene Glycol, and Isopropanol

An increased plasma osmolar gap characterizes intoxication with any of these 3 agents [11, 12]. Methanol and ethylene glycol also are associated with a high anion gap acidosis. Isopropyl alcohol, by contrast, affects acid-base status with far less frequency unless hypotension and tissue hypoxia ensue after ingestion.

Cardinal features which should alert physicians to suspect intoxication with these atypical alcohols are shown in Table 5. In addition to these characteristics, several other features are associated with atypical alcohol poisoning. Methanol and ethylene glycol may cause myoglobinuric acute renal failure (ARF). Methanol also can interfere with serum creatinine determinations while isopropanol can lead to spurious elevations in serum creatinine.

Despite the fact that intoxication with atypical alcohols results in an increased osmolar gap, the most common etiology for an elevated osmolar gap in clinical practice remains ethanol intoxication. Because ethanol ingestion may accompany intoxication with any of these agents, it is important to correct for the contribution of ethanol in determining the concentration of the toxin ingested. The equations for this calculation are shown in Table 6. These formulas serve to estimate the amount of toxin ingested.

Each of these alcohols manifests differences in toxicity and pharmacology [8]. The amount of methanol necessary to cause toxic-

Table 5. Cardinal Features of Intoxications with Atypical Alcohols

Clinical features

– METHANOL: Blurring of vision, “snowstorm” photophobia, blindness, sluggish or non-reactive dilated pupils, hyperemia of optic discs, retinal edema, and painful abdominal crisis due to pancreatitis.

– ETHYLENE GLYCOL: Alcohol-like intoxication without alcoholic fetor, “triphasic” clinical picture, urine sediment with abundant calcium oxalate crystals, and hypocalcemia.

– ISOPROPANOL: Acetonemia or acetonuria combined with fruity breath but no hyperglycemia or glycosuria.

Biochemical features

– Increased plasma osmolal gap.

– High anion-gap metabolic acidosis (methanol and ethylene glycol).

– Usually no change in acid-base status with isopropyl alcohol (unless hypotension and lactic acidosis prevail).

Table 6. Utility of the Osmolar Gap in Management of Intoxications

Substance	Structure	Molecular Weight	Lethal Level mg/dL	Corresponding Δ Osm
Ethanol	CH_3CH_2OH	46	350	76
Isopropanol	CH_3CHCH_3	60	340	56
Methanol	CH_3OH	32	80	25
Ethylene Glycol	CH_2-CH_2 OH OH	62	21	3.4
Acetone	CH_3-CO-CH_3	58	55	9.4

$$\text{Concentration of toxin (mg/dL)} = \frac{\Delta \text{ OsmX} \times \text{MW of X (mOsm/kg)}}{10}$$

where Δ OsmX = $\Delta \text{Osm}_{\text{total}} - \Delta \text{Osm}_{(\text{ethanol})}$

$$\Delta \text{Osm}_{\text{total}} = \text{“measured Osmolality”}^{*} - \text{“Calculated Osmolality”}^{+}$$

(*) by freezing point depression (LAB); (+) by formula $[2 \times \text{Na} + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}]$

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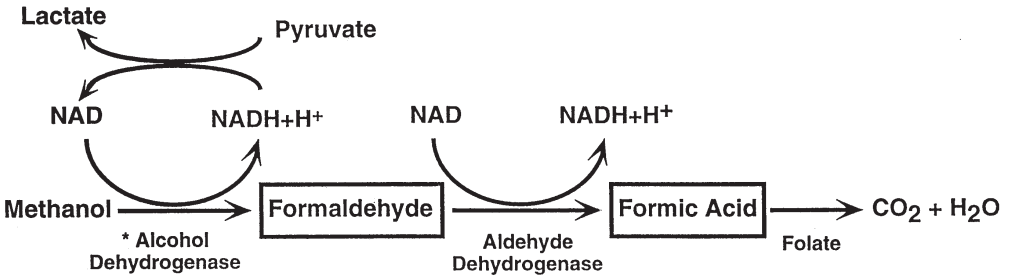

Figure 2. Methanol metabolism. Asterix indicates rate-limiting step. The affinity of methanol to alcohol dehydrogenase is only 1/10 the affinity of ethanol.

ity and death is variable, ranging from as little as 15 – 30 mL of a 40% solution to 60 – 240 mL. Death usually results at blood levels of 80 – 100 mg/dL (24 – 30 mmol/L). Serum methanol levels do not correlate well with prognosis; however, the degree of acidosis and serum formic acid levels are good predictors of mortality [19].

Peak blood levels of methanol occur 30 – 90 min after ingestion. Its V_d is 0.6 L/kg. Less than 5% of methanol is excreted unchanged by the kidney while the remaining 90 – 95% is excreted via hepatic metabolism (Figure 2). Alcohol dehydrogenase converts methanol to formaldehyde. This reaction, when it occurs in the retina, is responsible for the ocular toxicity associated with methanol poisoning [15]. Subsequently, formaldehyde is converted to formate by aldehyde dehydrogenase and other enzymes. Because ethanol has a 7 – to 10-fold fold greater affinity for alcohol dehydrogenase than methanol, it is used clinically to slow the metabolic transformation of methanol to its toxic product, formate.

The elimination $t^{1/2}$ for methanol in mild intoxications is 14 – 20 hours, but this increases to 24 – 30 hours in severe intoxications and 30 – 35 hours with the administration of ethanol. With ethanol and HD, this falls markedly to 2.5 hours [20].

Drowsiness is present early in methanol intoxication. A latent period follows (6 – 30 hours), but ends with the onset of the classical signs and symptoms of methanol poisoning: vomiting, vertigo, abdominal pain, change in vision, coma, and death [15].

Laboratory abnormalities associated with methanol ingestion include high osmolar and anion gaps as well as formic and lactic acidosis. The acidoses result from trapping of nicotinamide-adenine dinucleotide (NAD^+) as its reduced form (NADH) in the liver as a consequence of the oxidation of methanol to formic acid. This leads to an increase in formic acid concentration which reverses the normal oxidation of lactate to pyruvate; thereby, increasing blood lactate levels (Figure 2). Patients also may have hyperglycemia, an elevated hematocrit (HCT) and mean corpuscular volume (MCV), and an increase in serum amylase.

Treatment for methanol intoxication should be initiated as early as possible. Gastric lavage may be of benefit if the patient is seen early (< 2 hours) after ingestion. Ethyl alcohol should then be administered PO, IV, or via nasogastiric tube (NG) at a loading dose of 0.6 g/kg followed by a maintenance dose to achieve serum ethanol levels > 100 mg/dL (see Table 7). The metabolic acidosis also should be corrected readily [20, 21].

HD is indicated for methanol poisoning when the following are present:

Table 7. Guidelines for the Use of Ethanol in the Treatment of Atypical Alcohol Intoxications

- Maintain serum ethanol levels during treatment > 100 mg/dL
- Loading dose = 0.6 g/kg PO, NG, or IV
- Maintenance dose
  a. Alcoholic patient = 154 mg/kg/hour
  b. Non-alcoholic patient = 66 mg/kg/hour
  c. Double dose during hemodialysis
- PO or NG ethanol concentrations should not exceed 20%. IV ethanol is usually given as 10% ethanol in D_5W
- Continue ethanol until ethylene glycol or methanol are no longer detectable

- methanol blood levels > 50 mg/dL,
- visual, funduscopic, or mental status changes,
- severe metabolic acidosis,
- increased serum formic acid levels, or
- the patient consumed > 30 mL methanol [21].

Optimal dialysis can be achieved with a HCO_3^- dialysate bath, blood flows > 300 mL/min, and a large surface area dialyzer (1.5 m^2). HD should be continued until serum methanol levels are < 20 mg/dL. Folic acid may promote catalase-mediated formate metabolism to carbon dioxide (CO_2) and water and can be used at 2 mg PO daily. Finally, PD is an alternative if HD is not available.

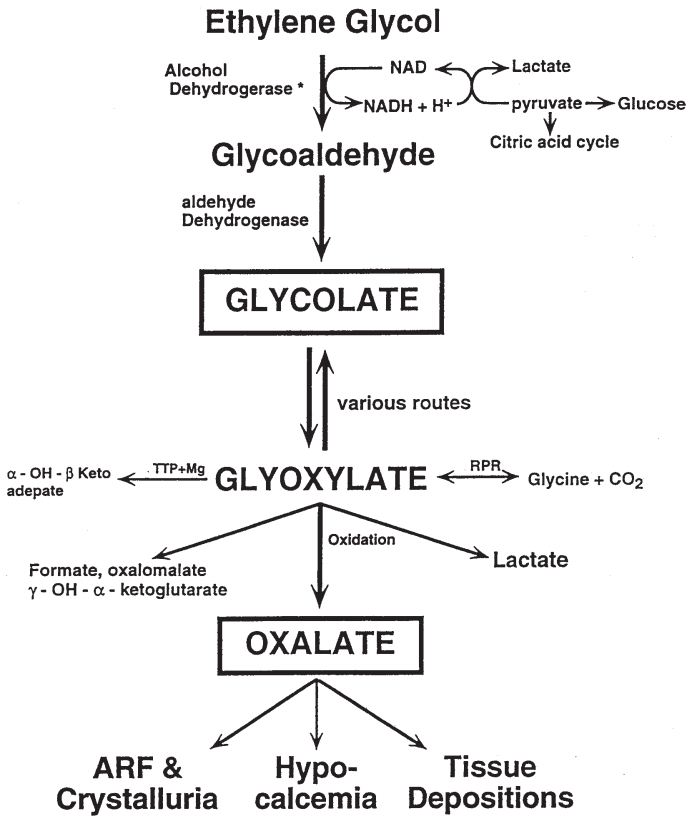

Figure 3. Ethylene glycol metabolism. Asterix indicates rate-limiting step. Ethanol has 100 × more affinity than ethylene glycol to alcohol dehydrogenase. TTP = thiamine as cofactor, PRP = pyridoxine as cofactor

Ethylene glycol has a V_d (0.6 L/kg) and lethal dose (100 mL) similar to methanol. Peak blood levels occur after 1 – 4 hours post-ingestion. Ethylene glycol is metabolized via alcohol dehydrogenase to several toxic compounds, including glycolic and oxalic acids (Figure 3). Alcohol dehydrogenase also has a far greater affinity for ethanol (100-fold) than ethylene glycol; hence, its administration is effective in delaying the breakdown of ethylene glycol to its toxic metabolites [13, 14].

The degree of toxicity and acidosis correlate best with the accumulation of glycolic acid; however, lactate production also may contribute to the metabolic acidosis. The $t^{1/2}$ for ethylene glycol without treatment is 3 – 8.5 hours; however, with ethanol treatment, it is 10 – 102 hours. Combined ethanol use and HD, as in the case of methanol ingestion, significantly shortens the elimination $t^{1/2}$ to 2.5 – 3 hours [22].

The clinical syndrome of ethylene glycol poisoning usually follows a triphasic course [14]. The earliest findings are neurologic abnormalities ranging from drunkenness to coma (Stage I). These are succeeded by pulmonary edema, cardiomegaly, and heart failure (Stage II). Acute tubular necrosis (ATN) occurs in the final stage (Stage III). This may be accompanied by calcium oxalate crystals in the urine and diverse laboratory abnormalities including: high osmolar and anion gaps, acidosis, leukocytosis, cerebrospinal fluid (CSF) xanthochromia, hypocalcemia, elevated creatine phosphokinase (CPK) and elevated liver function tests.

Therapy for ethylene glycol poisoning proceeds along many of the same guidelines outlined above for methanol intoxication. Initial treatment should entail gastric lavage and ethanol (see Table 7) as well as correction of the metabolic acidosis. An alternative to ethanol is fomepizole (4-methyl-pyrazole), a potent inhibitor of alcohol dehydrogenase [23, 24]. Treatment with fomepizole should be initiated as quickly as possible when there is a suspicion of ethylene glycol poisoning or a documented serum ethylene glycol concentration > 20 mg/dL. A loading dose of 15 mg/kg IV should be given, followed by doses of 10 mg/kg IV every 12 hours for 48 hours, then 15 mg/kg IV every 12 hours thereafter until ethylene glycol levels fall < 20 mg/dL. Fomepizole induces its own metabolism via the cytochrome P450 system, necessitating the increase in maintenance dose after 48 hours. The drug is dialyzable and its dosing must be intensified during HD. Preliminary data suggest that fomepizole is usually well tolerated but occasionally produces headache, nausea, dizziness, eosinophilia, or mild transient elevation of liver enzymes. Small studies or case series have documented prolongation of the $t^{1/2}$ of ethylene glycol from 3 – 16 hours and dramatic improvements in acidemia when the drug is administered. Fomepizole also prolongs the $t^{1/2}$ of ethanol, and the simultaneous use of both agents is not recommended.

Hypocalcemia also should be corrected if present. Hemodynamic monitoring may be necessary if the patient develops pulmonary edema or renal failure. IV fluids and mannitol should be given to patients without oligoanuria or pulmonary edema to maintain good urine output.

The 2 antidotes for ethylene glycol toxicity are pyridoxine which stimulates glyoxylate to glycine; and thiamine which hastens the metabolism of glyoxylate to α–OH ketoadipate. Pyridoxine should be given 500 mg intramuscularly (IM) 4 times daily and thiamine 100 mg IM 4 times daily. HD is indicated for a serum ethylene glycol level > 20 mg/dL or severe metabolic acidosis. Dialysis should be continued until the ethylene glycol level is < 20 mg/dL and the acidosis has resolved.

Isopropanol has a lethal dose between 150 – 240 mL. Life-threatening plasma levels approximate 400 mg/dL; nonetheless, clinical signs and symptoms are more reliable prognostic indicators than serum levels. Isopropyl alcohol is completely absorbed by 2 hours post-ingestion with an apparent V_d of 0.6L/kg. The elimination $t^{1/2}$ is 2.5 – 3.2 hours. Isopropanol undergoes oxidative metabolism by alcohol dehydrogenase to acetone which is excreted predominantly by the kidneys and, in part, by the lungs. Twenty to 50% of isopropanol does not undergo metabolism and is excreted directly by the kidneys. A proportion of absorbed isopropanol is re-secreted into saliva and stomach and hence the value of repeated MDAC even after its absorption.

Isopropanol, like the aforementioned atypical alcohols, is a CNS and myocardial depressant. Hemorrhagic gastritis, profound hypotension, hypothermia, and hypoglycemia also may complicate isopropanol ingestions. Hypotension also is important because this plays a critical factor in determining patient prognosis after isopropanol ingestion [18].

Therapy for most patients with isopropanol intoxication focuses upon supportive measures including IV fluids, pressor agents and mechanical ventilation, if necessary, as well as symptomatic treatment for GI distress. HD is of great benefit, effectively removing isopropanol and acetone from the plasma. The indications for HD are: 1) plasma levels > 400 mg/dL, 2) prolonged coma, 3) hypotension, 4) myocardial depression and tachyarrythmias, and 5) renal or hepatic failure [18].

Lithium Intoxication

Lithium carbonate is a valuable and widely-used drug in the treatment of bipolar affective disorders. However, this medication has a low therapeutic index and can induce a multitude of adverse and even, life-threatening complications. Acute overdose has a mortality rate approaching 25%. In contrast to many other drug poisonings, acute lithium intoxication usually results from chronic accumulation [8, 25, 26]. The clinical manifestations of toxicity such as neuromuscular irritability, mental status changes, and hypotension are often superimposed on the drug's chronic effects e.g. nephrogenic diabetes insipidus, renal acidification defects, interstitial nephritis, and goiter [25, 26].

Patients taking lithium who have polyuria are prone to lithium intoxication when they are unable to maintain an adequate fluid intake and, hence, suffer dehydration [27]. Old age also places patients at greater risk for lithium toxicity as a result of diminished renal clearance and V_d [28]

Lithium carbonate and lithium citrate are readily absorbed from the gastrointestinal tract with peak serum levels 2 – 4 hours after ingestion. Lithium is freely distributed in whole body water with a V_d of 0.8 L/kg. Steady-state plasma levels usually are reached within 5 days during conventional oral dosing (1200 – 1800 mg/day) [27].

Lithium is predominantly excreted by the kidney. Following filtration, 75 – 80% of filtered lithium is reabsorbed in the proximal tubule while the remainder is excreted in the urine. Any process which increases proximal tubule sodium reabsorption, e.g. extracellular volume depletion, decreases the renal clearance of lithium and thus, may necessitate a dosage change. The usual $t^{1/2}$ approximates 18 hours in young adults and increases to 36 hours in the elderly. Given these extended $t^{1/2}$, blood levels for monitoring serum lithium should be drawn no earlier than 12 hours after the last dose [27].

The clinical manifestations of lithium toxicity may be subtle especially during its prodromal phase. However, a good correlation

Table 8. Indications for Hemodialysis in Lithium Toxicity

- Serum lithium> 3.5 mEq/L regardless of patient presentation.
- Serum lithium > 2.5 mEq/L and,
  Markedly symptomatic patient
  Renal insufficiency
  Presence of condition(s) that increase renal sodium avidity (cardiac failure, cirrhosis).
- Serum lithium = 2.5 – 3.5 mEq/L, but asymptomatic
  Consider HD if serum lithium is not anticipated to be < 0.6 mEq/L by 36 hours.

exists between the symptomatology of lithium toxicity and serum lithium levels [29]. Mild (serum level = 1.5 – 2.5 mmol/L) and moderate (serum level = 2.5 – 3.5 mmol/L) lithium toxicity are characterized by neuromuscular irritability, weakness, delirium, nausea, emesis, and diarrhea. Sinus bradycardia and hypotension can also occur. Severe toxicity (serum level > 3.5 mmol/L) can result in seizures, stupor, coma, and a 10% risk of permanent neurologic sequelae, e.g. dementia or ataxia. Laboratory manifestations of lithium intoxication include a decreased serum anion gap (lithium is an unmeasured cation) and leukocytosis [25].

Recognizing and avoiding states predisposing to lithium intoxication are the best strategy for preventing this drug's significant toxicity. Nonetheless, some patients will develop acute lithium poisoning and require treatment commensurate with the adequacy of their renal function and the degree of intoxication. Initial therapeutic measures include the withdrawal of any concomitant diuretic therapy. These may be re-introduced, after correction of intravascular volume depletion, to control nephrogenic diabetes insipidus. Patients with cardiac disease, arrhythmias, or severe toxic reactions, e.g. obtundation, should be monitored in an intensive care unit (ICU). Maximizing lithium clearance by restoring sodium and water balance is essential. While administering IV fluids, it is important to avoid hypernatremia, therefore 0.45% NaCl solution (half-normal saline) or another hypotonic solution is advisable. Forced diuresis and large volume saline infusions have limited applications in the treatment of lithium toxicity unless the glomerular filtration rate (GFR) is reduced. Evidence suggests that the fractional excretion of lithium (FE_{Li})does not change consistently during saline administration unless hypovolemia and a depressed GFR are already present [27].

HD remains the therapy of choice for severe lithium toxicity. HD rapidly reduces serum drug levels and the $t^{1/2}$. The indications for HD are summarized in Table 8 [27, 30, 31]. HD effectively clears lithium at nearly 50 mL/min compared to 15 mL/min for PD. However, because intracellular lithium re-equilibrates slowly, serum levels may rebound after the cessation of dialysis. Continued or delayed gastrointestinal absorption related to sustained-release lithium formulations may also contribute to this rebound in serum levels. Extending the duration of dialysis can obviate this phenomenon. Generally, a 9-hour HD session removes 60% of the total lithium burden. One strategy is to perform dialysis for 8 – 12 hours initially and repeat dialytic treatments as necessary until the serum Li remains < 1.0 mmol/L, 6 – 8 hours post-dialysis. An alternative is simply a 6-hour HD with a large surface area dialyzer, reducing serum lithium to the desired level. Continuous arteriovenous hemodiafiltration (CAVHDF) may also prove to be a safe and efficacious therapy by significantly augenting lithium excretion [32, 33].

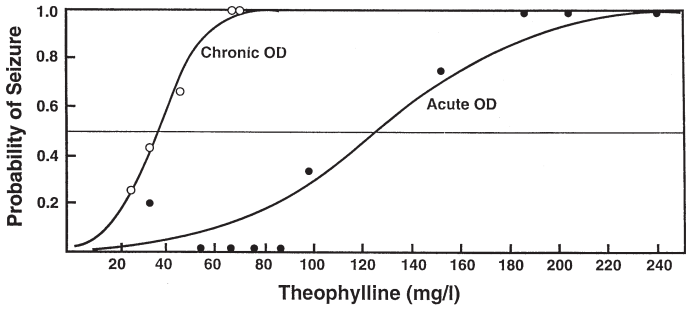

Figure 4. Probability of seizures as a function of peak measured theophylline concentration for acute single injection versus chronic overmedication. OD = overdose. Adapted from Olson, Am. J. Emerg. Medicine 1985; 3:386.

Theophylline Toxicity

Severe theophylline toxicity is associated with significant morbidity and mortality as a result of sustained or recurrent seizures, hypotension, and arrhythmias. With the extensive use of sustained-release theophylline products, prolonged toxicity is possible. Although the symptomatology of theophylline toxicity relates to the serum concentration, there is no predictable step-wise relationship between these factors. Nonetheless, 30% of patients with serum theophylline concentrations > 15 mg/mL will have mild toxicity, while toxic reactions will be present in 78% of patients with levels > 25 mg/mL (therapeutic, 10 – 20 mg/mL). The "acuteness" or "chronicity" of the intoxication also will affect the severity of symptoms (Figure 4). At any given serum level, chronic intoxication will have more pronounced manifestations than acute intoxication [34].

Many factors influence the development of theophylline toxicity by decreasing drug metabolism [35]. Significant cardiac or hepatic disease and concurrent drug use (erythromycin, cimetidine, ciprofloxacin, cephalexin, tetracycline, oral contraceptives, allopurinol, propranolol, and thiabendazole) can delay the metabolic clearance of theophylline, as can old age and early infancy (< 6 months).

Seizure activity may occur with serum theophylline concentrations as low as 25 mg/mL, but, more commonly at concentrations > 40 mg/mL. Seizures can occur many hours after the peak serum theophylline level in acute intoxications. The reason for this temporal discrepancy is unknown. Unexpected seizures may be the presenting clinical finding in chronic intoxication [34, 36]. Tachyarrythmias can occur with serum theophylline levels > 20 – 30 mg/mL. Cardiovascular collapse and respiratory arrest however, are rare unless the concentration is > 50 mg/mL in chronic overdose, or > 100 mg/mL in acute toxicity [36]. Metabolic abnormalities often accompany theophylline toxicity including hypokalemia, hypomagnesemia, hypophosphatemia, hypercalcemia, hyperglycemia, and respiratory alkalosis [37].

Theophylline is slightly more than 50% protein bound with a small V_d (0.4 – 0.6 L/kg). It is extensively metabolized by the hepatic cytochrome P-450 system with only 8 – 10% excreted unchanged in the urine. At therapeutic doses, blood levels follow first-order kinetics but at toxic levels, mixed first-order and zero-order kinetics prevail. The implications of a small V_d, rapid blood-tissue equilibration, and a prolonged $t^{1/2}$ due to low intrinsic clearance, are that a substantial amount of drug can be removed during a HD or HP session [35, 36].

Table 9. Indications for Extracorporeal Therapy in Theophylline Toxicity

- Seizures and/or arrhythmias with cardiovascular instability.
- Acute intoxication with plasma theophylline level ≥ 100 mg/L (550 μmol/L), or levels approaching 100 mg/L in 2 hours.
- Chronic intoxication in a patient over age 60 years with plasma theophylline level > 40 mg/L (220 μmol/L).
- Chronic intoxication in a younger patient with plasma theophylline level > 60 mg/L (300 μmol/L) and who cannot tolerate multiple doses of activated characoal or has other risk factors for major toxicity.
- Any intoxication with levels > 60 mg/dL in a patient who is at risk of seizure or has other medical complications:
  1. Impaired theophylline metabolism (chronic liver disease, CHF, hypoxemia (PO_2 < 40 mmHg), or neonate).
  2. History of epilepsy.
  3. Ischemic heart disease or severe chronic lung disease.

The mainstays for treating theophylline toxicity are supportive measures and oral activated charcoal [36, 38, 39]. The latter is indicated even for IV intoxications. Activated charcoal is administered 1 g/kg initially followed by 20 g every 2 hours for 6 – 12 hours. A cathartic such as sorbitol (50 – 75 mL of 70% solution) should also be considered. There are no firm indications for HD or HP. Table 9 lists well-accepted guidelines for the performing HP in theophylline toxicity. Most authors however, agree that either extracorporeal therapy is indicated for unstable patients with seizures, hypotension, or arrhythmias [36, 38, 40] (Table 9). Acute toxicity with serum theophylline levels > 100 mg/mL, chronic intoxication with a level > 60 mg/mL in a young person, or chronic intoxication with a level > 40 mg/mL in an individual older than 60 all warrant either HD or HP. Serial HD-HP (a dialysis membrane followed by a HP cartridge in the extracorporeal circuit) offers the advantage of each modality and delays saturation of the HP cartridge [41].

Other therapies also have demonstrated some efficacy in theophylline toxicity, albeit, in small studies or case reports. Plasmapheresis [42] has succeeded in lowering serum theophylline concentrations in children and exchange transfusion [43] has been beneficial in treating theophylline intoxication in infants and neonates. Further experience with these techniques will be necessary to assess their absolute effectiveness. Finally, when HD or HP are not available, it is reasonable to consider continuous arteriovenous or venovenous hemofiltration (CAVHF or CVVHF) to clear theophylline [9]. However, an extended treatment course is required to accomplish effective drug clearance due to the lower blood flow inherent in these techniques.

Salicylate Intoxication

Salicylate poisoning is a frequent and often overlooked cause of drug intoxication. Salicylate toxicity annually is responsible for 10% of intoxication-related deaths and 14% of severe intoxications in the United States. The most common form of salicylate is aspirin. Other sources include methyl salicylate (oil of wintergreen), sodium salicylate, salicylic acid, and many over-the-counter preparations.

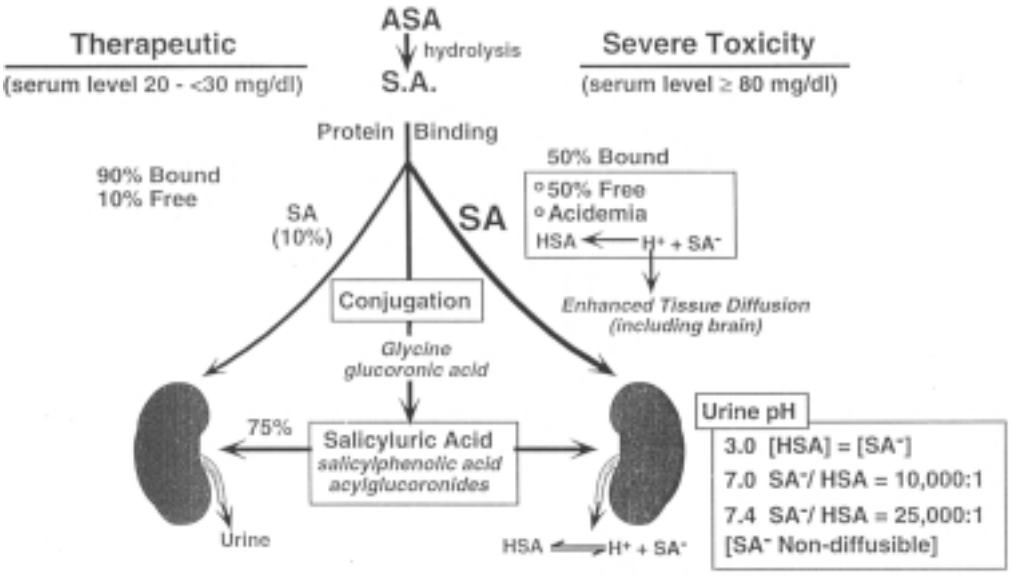

Figure 5. Biochemical basis of salicylate toxicity and its therapy. ASA = acetylsalicylic acid, SA = salicylic acid. ASA is rapidly converted to SA, and this metabolite exert the drug's toxic effects. At therapeutic levels 90% of salicylate is protein bound and thus, confined to the intravascular space. Subsequently, SA is 75% glycinated in the liver to salicyluric acid which is less toxic and excreted more rapidly by the kidney than SA. When salicylate toxicity occurs (serum levels > 40 mg/dL), the extent of protein binding declines and salicyluric acid formation becomes saturated. Salicylate concentrations increase and, with a fall in renal excretion, drug $t^{1/2}$ prolongs from 3 – 12 hours to 15 – 30 hours.

Several narcotic or sedative compounds also are prescribed in combination with salicylates. These include oxycodone (Percodan), propoxyphene (Darvon), and barbiturate (Fiorinal).

Acetylsalicylic acid is rapidly converted after ingestion to salicylic acid and this metabolite exerts the drug's toxic effects (Figure 5). At therapeutic levels (20 – 30 mg/dL), 90% of salicylate is protein bound and thus, confined to the intravascular space. Subsequently, salicylic acid is 75% glycinated in the liver to salicyluric acid which is less toxic and excreted more rapidly by the kidney than salicylic acid. When salicylate toxicity occurs (serum levels > 40 mg/dL), the extent of protein binding declines and salicyluric acid formation becomes saturated. Salicylate concentrations increase and, with a fall in renal excretion, drug $t^{1/2}$ prolongs from 3 – 12 hours to 15 – 30 hours [44].

A dose of 150 mg/kg is usually associated with toxicity. This roughly equates to 35 tablets or 10 g in an adult. Fatalities have occurred in adults after ingesting 10 – 30 g and, in children after doses of 3 g. Early symptoms of toxicity include tinnitus, vertigo, nausea, vomiting, and diarrhea. Severe intoxication can result in altered mental status, coma, noncardiogenic pulmonary edema and death.

A variety of acid-base disturbances accompany salicylate intoxication [45]. Salicylates directly stimulate the respiratory center resulting in a rapid fall in the pCO_2 and respiratory alkalosis. A high anion gap metabolic acidosis may ensue, primarily as a result of the accumulation of organic acids, including lactate and ketoacids. The respiratory alkalosis

normally promotes lactic acid production to counteract the pH increase, and this augents the development of the acidosis. Salicylic acid (MW 138) itself contributes only minimally to the acidosis since a plasma level of 50 mg/dL is equivalent to < 3 mEq/L.

The result of these metabolic changes is that most adults with salicylate intoxication have either a respiratory alkalosis or a mixed respiratory alkalosis-metabolic acidosis. A pure metabolic acidosis is highly unusual except in children. An acute respiratory acidosis also can occur, especially if the patient has ingested other medications or has progressed to severe toxicity.

An accurate diagnosis of salicylate intoxication is often suspected from the history and the presence of acid-base disturbances. Rapid diagnosis also can be culled from the urinalysis. A positive serum Phenistix (brown discoloration with phenothiazines or salicylates > 700 mg/mL) or a positive urine ferric chloride test (purple color when 4 drops ferric chloride are added to 1 mL urine) are strongly suggestive of salicylate intoxication. Confirmation of the diagnosis is made by measuring plasma drug levels [46].

The serious toxicity of salicyclates is related to their tissue concentrations. Therefore, initial therapeutic objectives are aimed at reducing drug absorption by administering activated charcoal (50 g every 3 hours) and decreasing drug accumulation by systemic alkalinization. $NaHCO_3$ (2 ampules in 1L D_5W) should be given to raise the arterial pH to 7.45 – 7.50. This promotes a marked reduction in tissue salicylate concentrations.

The next goal of therapy is rapid drug elimination. Urinary alkalinization is important to pursue as it increases salicylate removal. Salicylate primarily enters urine through the organic anion secretory pathway in the proximal tubule. The rate of salicylate excretion can be markedly enhanced by urine alkalinization. $NaHCO_3$, administered as above, should be targeted to raise the urinary pH to 7.5 – 8.0. This can increase salicylate excretion up to 5-fold. Acetazolamide, a carbonic anhydrase inhibitor, also induces a bicarbonate diuresis by inhibiting proximal bicarbonate reabsorption. However, urinary HCO_3^- loss will lead to an undesired fall in systemic pH, thereby increasing salicylate entry into the brain and aggravating the toxic state. Acetazolamide therefore is not advocated as sole therapy for aspirin intoxication and should rarely be considered, only in concert with $NaHCO_3$ therapy, once systemic acidemia has been corrected [44, 47].

HD also is highly efficacious for treating salicylate toxicity. Save for its extensive protein binding, salicylate satisfies the criteria for toxins readily removed by HD. This modality should be utilized when plasma salicylate concentrations are > 80 mg/dL, especially in the presence of impaired renal function. It should also be implemented in the setting of salicylate intoxication with volume overload (compromising $NaHCO_3$ administration), coma, or progressive clinical deterioration. Finally, HD also is indicated to correct the acid-base and fluid and electrolyte disturbances which may occur in salicylate poisoning, especially in patients with renal failure [8].

Valproic Acid Intoxication

Valproic acid is an effective anti-epileptic drug, often used for simple and complex absence (petit mal) seizures. In spite of its efficacy, accidental or intentional overdose with valproic acid can cause serious toxicity and even death.

Valproate sodium is readily converted to valproic acid after ingestion in the stomach. The drug is rapidly and almost completely

absorbed from the GI tract with peak serum levels 1 – 4 hours after ingestion for valproate sodium and 3 – 5 hours after a single oral dose of divalproex sodium. Valproic acid demonstrates significant protein binding (80 – 90%) and achieves a V_d of 0.1 – 0.5 L/kg. It manifests first-order kinetics with an elimination $t^{1/2}$ of 5 – 20 hours, although this may extend to > 30 hours in the setting of valproate intoxication. Valproic acid is primarily metabolized by the liver with glucuronide conjugates excreted by the kidney. Only small amounts of drug are excreted unchanged in the urine.

Therapeutic plasma concentrations for valproic acid have not been well established, but 50 – 100 mg/mL may be an appropriate target for patients taking 1.2 – 1.5 g of valproic acid daily. Drug toxicity with valproate is variable, ranging from nausea, vomiting, and indigestion to CNS changes encompassing lethargy, drowsiness, and coma. Patients may have elevated serum transaminase levels, hyperammonemia, and an apparent bleeding diathesis with petechiae, ecchymoses, and a prolonged bleeding time. Some individuals also may have a false positive urine test for ketones related to one of the valproate metabolites.

Treatment for valproic acid intoxication has classically centered around early gastric lavage and activated charcoal followed by forced diuresis. This however, has had limited utility given the small amount of valproic acid excreted unchanged in the urine. While no immediate antidotes are available for this drug, several studies have outlined successful combination HD / HP treatment in valproic acid poisoning. Though these are primarily case reports, they suggest that HD performed "in series" with HP can rapidly lower serum valproate levels and, possibly, stave off the ill effects of drug toxicity [48]. The efficacy of valproic acid removal by HD increase in the overdose setting. At blood levels > 90 – 100 mg/mL, protein binding sites become saturated, leading to a progressive increase in free valproic acid concentrations and, thus, enhanced clearance across dialysis membranes. Successful removal of valproic acid has been reported especially when HD has been initiated at plasma drug concentrations of 700 – 750 mg/mL [49]. A report from the University of Texas Southwestern Medical Center also has proposed that higher blood flows may contribute to the rapid and significant valproic acid extraction achieved during extracorporeal therapy [48]. With these limited data, it is difficult to standardize the indications for dialytic and/or HP therapy in valproic acid intoxication. It is reasonable however, to suggest that HD at blood flows of 300 – 350 mL/min with or without HP may benefit patients who are profoundly ill (CNS toxicity, bleeding diathesis, increased serum transaminases, increased serum ammonia level, and increased bleeding time).

Intoxications Less Responsive to Extracorporeal Therapies

Acetaminophen Toxicity

Acetaminophen is a remarkably safe drug when used at normal therapeutic doses. Massive acute overdose however, can result in fulminant hepatic failure and death [50]. Fortunately, the antidote for acetaminophen intoxication, N-acetylcysteine, can prevent fatalities, if administered in a timely fashion [51]. Thus, prompt recognition of acetaminophen overdose and rapid institution of therapy are of the utmost importance.

At therapeutic doses (10 – 15 mg/kg/dose in children; 325 – 1000 mg/kg/dose in adults) 90% of acetaminophen is metabolized in the liver to sulfated and glucuronide conjugates that are excreted in the urine. The remaining 10% is metabolized by the cytochrome CYP2E1 (P450 2E1) mixed function oxidase pathway to a toxic intermediary N-acetylimidoquinone NAPQI). Normally, this compound is then conjugated with hepatic glutathione to form a non-toxic mercapurate. With toxic doses, the sulfate and glucuronide pathways become saturated and an increased acetaminophen fraction is metabolized by cytochrome P-450 mercapturic acid utilizing glutathione. Once glutathione is depleted to < 70%, N-acetylimidoquinone begins to accumulate. This compound covalently binds hepatic macromolecules and, ultimately results in hepatocyte lysis [52].

In addition to the toxic effects of NAPQI, a rat model of hepatotoxicity suggests that nitric oxide also may contribute to the hepatic injury [53]. In this model, acetaminophen increased nitric oxide production via enhanced expression of inducible nitric oxide synthetase. Furthermore, the hepatic injury was substantially ameliorated by treatment with aminoguanidine which by inhibiting inducible nitric oxide synthase, reduced nitric oxide production. This benefit was achieved without change in CYP2E1 protein expression or NAPQI formation.

Within 2 – 12 hours after acetaminophen poisoning, patients may have nausea, emesis, diaphoresis, lethargy, and malaise. Temporary symptomatic improvement may then ensue for the next 1 – 2 days. At this stage, some individuals manifest minor elevations in serum transaminases, a prolonged prothrombin time, and hepatomegaly with right upper quadrant pain. The hepatic stage usually begins 72 – 96 hours after ingestion when patients develop mental status changes, hyperammonemia, marked increases in hepatic enzymes, and a bleeding diathesis. Greater than 2-fold prolongation of the prothrombin time and/or serum bilirubin > 4 mg/dL on the 3rd – 5th day post-ingestion are indicative of severe hepatotoxicity.

At this stage, ARF also may appear, usually as a result of ATN. However, papillary necrosis can also occur. The overall incidence of renal dysfunction in acetaminophen overdose ranges from 5% (in patients without hepatic failure) to 53% (in patients with fulminant hepatic failure). The mechanism of nephrotoxicity may be similar to that of hepatotoxicity. A toxic intermediate is formed in situ in renal tissue via the P-450 pathway and binds covalently to renal macromolecules. This results in renal cell necrosis. Oliguric ARF usually occurs. Proteinuria and hematuria may also be evident 2 – 4 days after overdose. Recovery of renal function transpires 2 – 4 weeks after ingestion although some patients do require dialysis.

The diagnosis of acetaminophen intoxication is made by history and determining the serum acetaminophen level. This laboratory value (when obtained 4 – 24 hours after ingestion) should be plotted against the Rumack-Matthew nomogram (Figure 6) to establish the risk of hepatotoxicity and the need for N-acetylcysteine therapy [54]. Serum levels obtained before 4 hours may not represent peak levels.

Therapy for acetaminophen toxicity should begin with gastric decontamination and activated charcoal. Activated charcoal avidly adsorbs acetaminophen and should be administered to any patient who presents within 4 hours after ingestion to minimize the 4 hour plasma acetaminophen level. Charcoal then should be removed from the gastrointestinal tract since it also adsorbs N-acetylcysteine, the antidote for acetaminophen intoxication.

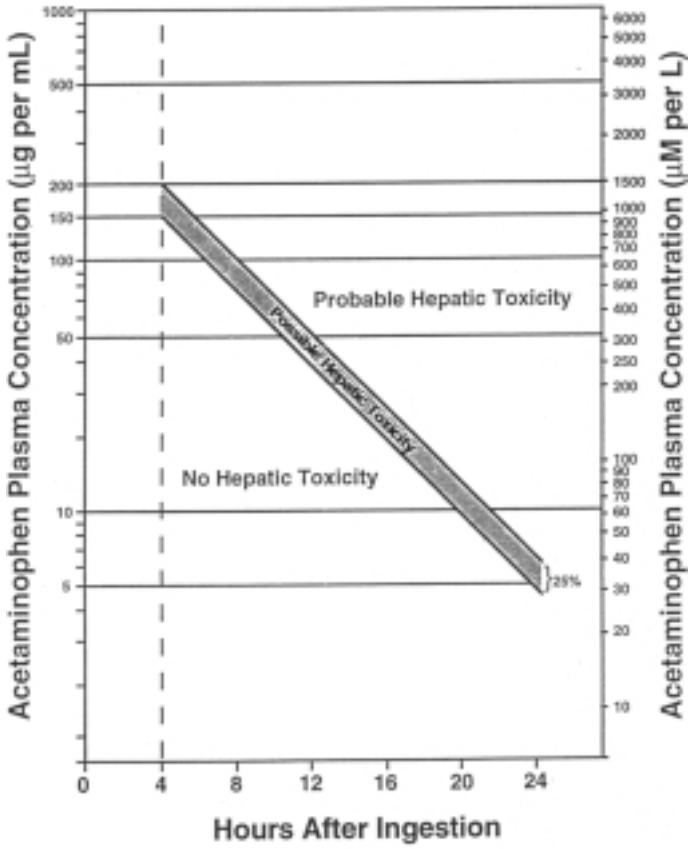

Figure 6. Rumack-Matthew nomogram for acetaminophen poisoning.

N-acetylcysteine is administered as a loading dose of 140 mg/kg of a 20% solution PO, NG or via orogastric tube (OG) followed by 70 mg/kg every 4 hours for 17 doses. Any doses vomited should be repeated. Treatment should be initiated within 8 – 10 hours after ingestion as the incidence of hepatotoxicity significantly increases when N-acetylcysteine therapy is delayed for > 10 hours post-ingestion. The efficacy of N-acetylcysteine therapy declines progressively if started 10 – 16 hours after ingestion, but some benefit is seen even if N-acetylcysteine cannot be initiated until 24 hours after ingestion.

To reduce nausea and vomiting that occur with N-acetylcysteine, given its "rotten egg" odor, the 20% solution can be diluted 1 : 3 with cola, orange juice, or grapefruit juice. Chilling the solution, slow NG administration or antiemetics also may decrease these side effects. IV N-acetylcysteine is available in the United States only for investigational studies. This mode of administration precludes the GIside effects and has been used successfully in Europe, Britain, and Canada [55].

N-acetylcysteine acts by enhancing glutathione stores, thus, providing a glutathione substitute. This, in turn, enhances non-toxic sulfate conjugation and prevents the accumulation of N-acetylimidoquinone. Aside from the aforementioned side effects, N-acetylcysteine administration has been associated with

bronchospasm, rhinorrhea, fever, chills, angioedema, hypotension, hemolysis, anaphylactoid reactions, and cardiovascular collapse.

HD and HP

The efficacy of acetaminophen removal by HD or HP in protecting against hepatic failure following acetaminophen has not been demonstrated [52, 56, 57]. As a result, these modalities are not recommended in the management of acetaminophen intoxication [44 – 46], with the possible exception of patients who present late in the course (> 24 hours) when N-acetylcysteine would be of limited value [58]. In this situation, HP may be associated with lesser elevation in plasma transaminases when compared to supportive therapy alone or to the administration of N-acetylcysteine. However, we do not use HP for an acetaminophen overdose, because the potential risks probably outweigh the slight benefit that might be achieved.

Digitalis Intoxication

Cardiac glycoside poisoning often results during chronic use. Indeed, one-half of life-threatening digitalis intoxications transpire during long-term digitalis therapy. The 2 preparations in clinical use today are digoxin and digitoxin. These drugs act at the cellular level to inhibit membrane-bound Na^+-K^+-ATPase. This results in the intracellular loss of K^+ ions and gain of Na^+ and Ca^{2+}. These compounds have excellent bioavailability ranging from 80% for digoxin to nearly 100% for digitoxin. Approximately 7% of digoxin and 26% of digitoxin is recycled through the enterohepatic circulation. The serum half-lives ($t^{1/2}$) for digoxin and digitoxin are 1.6 and 5 days, respectively [59].

Digoxin has a tremendous V_d (5.6 L/kg). Its major depot is skeletal muscle; dosage requirements and the likelihood of toxicity can be anticipated on the basis of muscle mass. A third of digoxin body stores are excreted daily (30% as digoxin in urine and 3% as metabolites in stool). By contrast, nearly 20% of digitoxin's total body stores are excreted daily, primarily as inactive metabolites [59].

Several factors predispose patients to digitalis toxicity. Cardiac medications such as quinidine, verapamil, and amiodarone increase serum digoxin levels. Erythromycin and tetracycline may increase digoxin levels by altering gut flora instrumental in digitalis metabolism. Another antibiotic, rifampin, reduces digoxin levels. Potassium-sparing diuretics increase drug levels by impairing tubular digoxin secretion. Old age, cardiac disease and metabolic disturbances, e.g. hypokalemia and hypomagnesemia, also alter patient sensitivity to digoxin and potentiate drug toxicity. Finally, renal dysfunction results in a decrease in renal digitalis excretion; thereby, increasing total body digoxin and prolonging the $t^{1/2}$ [59].

Digitalis toxicity has multiple and non-specific manifestations. They range from fatigue, blurred vision, and altered color perception to anorexia, nausea, emesis, and abdominal pain. CNS changes include headache, confusion, and delirium. The cardiac signs of digitalis toxicity encompass an array of arrhythmias, some life-threatening. The combination of supraventricular tachyrhythmia and atrioventricular block is highly suggestive of cardiac glycoside toxicity. Hypokalemia tends to aggravate digitalis toxicity especially in the setting of chronic intoxication whereas hyperkalemia usually results from acute overdosage [59].

Steady-state serum digoxin levels are reached 6 – 8 hours after administration; therefore, samples for drug monitoring should not be obtained until at least 6 hours after the last dose was administered. This interval may need to be extended to 12 – 24 hours in patients with renal failure given the prolonged $t^{1/2}$ for digoxin in this setting [59].

False positive elevations of serum digoxin levels can occur in patients with end-stage renal disease (ESRD), hepatobiliary disease, pregnancy, and in neonates [60]. These are believed secondary to elevations in endogenous digoxin-like substances The assay method can improve the specificity of serum digoxin measurements. Combined liquid chromatography/ radioimmunoassay significantly eliminates digoxin-like substance immunoreactivity as does centrifugal ultrafiltration prior to a fluorescence polarization immunoassay for digoxin [61].

Serum digoxin levels should only be used as an adjunct to clinical judgent for therapeutic dosing and recognition of toxicity. Patients can manifest clinical toxicity despite serum digoxin levels < 2 ng/mL whereas, some individuals may necessitate and tolerate digoxin therapy at serum levels between 2 – 3 ng/mL without overt signs of intoxication.

Successful treatment for digitalis intoxication depends upon early recognition. Once the physician recognizes digitalis toxicity, initial therapy should include the administration of activated charcoal to adsorb digitalis and its metabolites excreted via the biliary tract. Cholestyramine also can be used to decrease drug absorption especially if ingestion occurred within 6 – 8 hours. Measures to correct serum K^+ and other electrolyte imbalances are paramount. Acute digitalis poisonings often are complicated by severe hyperkalemia and may require treatment with sodium bicarbonate, insulin and glucose solutions, exchange resins, or even, dialysis.

Symptomatic bradyarrhythmias are appropriately treated with IV atropine (0.5 – 2 mg) and electrical pacing, if necessary. Other cardiovascular therapy, especially antiarrhythmic drugs and cardioversion, is reserved for more complex forms of cardiac ectopy.

Severe digitalis overdose may necessitate therapy with digoxin-specific antibody fragents (F_{ab} fragents) (Table 10) [62]. F_{ab} fragents, purified from sheep IgG, are indicated for massive digoxin ingestion, profound toxicity, or hyperkalemia in the presence of life-threatening arrhythmias associated with cardiac glycoside toxicity. These F_{ab} fragents rapidly bind intravascular digoxin and diffuse into the interstitial space to bind free digoxin. F_{ab}-bound digoxin cannot associate with the a-subunit of Na^+-K^+-ATPase and F_{ab} and drug molecule are thus, filtered at the glomerulus and rapidly excreted in the urine. F_{ab} fragents are also successful in patients with renal failure and dialysis. The theoretical possibility exists that digoxin could be released from the complex when excretion of F_{ab}-bound digoxin is delayed by renal failure. This could result in "rebound" digitalis toxicity. While this has been an infrequent occurrence in studies examining the utility of F_{ab} in patients with renal failure, at least one report has posited the benefit of plasmapheresis 24 – 40 hours after F_{ab} treatment in patients with renal failure to forestall this possibility [63].

F_{ab} treatment has been associated with untoward effects in approximately 10% of patients including exacerbations of congestive heart failure (CHF), tachyarrythmias, and hypokalemia. Allergic or anaphylactic reactions are rare, occurring in < 1% of treated patients, but skin testing is appropriate for individuals with known allergy to sheep proteins or those treated previously with F_{ab} [62].

HD or HP may help control hyperkalemia or volume overload; however, these approaches are generally inadequate for treating

Table 10. Determination of Equimolar Digoxin-specific F_{ab} Fragent Dose

– Steady-State serum concentration (SDC is known)
Total Body Load (TBL) = SDC × V_d × weight

$$\text{TBL (mg)} = \frac{\text{SDC(ng/mL)} \times 5.6\text{L/kg} \times \text{W (KG)}}{1000} [\text{Digoxin}]$$

$$\text{Eqimolar dose of Fab} = \text{TBL} \times \frac{\text{MW (50000)}}{\text{MW Digoxin (781)}}$$

$$= \text{TBL} \times 64$$

1 vial F_{ab} (40 mg) neutralizes 40/64 (or 0.6 mg digoxin)

$$\text{Therefore, \# Vials } F_{ab}\text{*} = \frac{\text{TBL (mg)}}{0.6}$$

$$\text{\# vials Fab} = \frac{\text{SDC (ng/ml)} \times \text{WT (kg)}}{100} [\text{Digoxin}]$$

$$\text{\# vials Fab} = \frac{\text{SDC (ng/ml)} \times \text{WT (kg)}}{1000} [\text{Digitoxin}]$$

– Amount ingested is known
Body load (mg) = Dose ingested (mg) [Digitoxin]; given a bioavailability of 100%
= Dose ingested (mg) × 0.8 [Digoxin]; given a bioavailability of 80%

– Amount ingested and SDC unknown
vials (F_{ab}) = 10, repeat 10 vials if clinically indicated (total 20 vials, adult, acute overdose)
chronic toxicity, SDC not known, give 6 vials (adult), 1 vial (children)

*Reconstitute each vial in 4 mL sterile water and administer total dose intravenously over 15 – 30 min. In cardiac arrest dose can be given as a bolus.

digitalis toxicity secondary to the drug's extensive tissue binding and large V_d.

Procainamide Toxicity

The pharmacokinetics of procainamide and its major metabolite, N-acetylprocainamide (NAPA), are significantly altered in patients with chronic renal failure. The usual therapeutic plasma concentrations of procainamide range from 4 – 8 mg/L and for NAPA, 9 – 20 mg/L. Cardiotoxicity can occur with concentrations of procainamide as low as 10 mg/L and is common at concentrations > 16 mg/L. Plasma concentrations of procainamide be-

tween 20 – 30 mg/L frequently cause serious hypotension and conduction disturbances and have been implicated in several deaths [64]. Combined levels of procainamide and NAPA > 60 mg/L can cause severe cardiac toxicity, profound hypotension and lethargy [65]. The main route of elimination of procainamide and NAPA is renal, with 60%and 80% excreted unchanged, respectively.

In addition to renal failure, several drugs, either by inhibiting the metabolism of procainamide or its renal excretion, or through pharmacodynamic interactions, especially class IA drugs, may increase the toxicity of procainamide. These include amiodarone, cimetidine, quinidine, trimethoprim, calcium channel blockers, and tricyclic antidepressants (TCA).

Treatment

Because procainamide and NAPA are substantially eliminated by the kidney, it is important to maintain adequate renal function in patients intoxicated with these drugs. Optimizing cardiac function and aggressive treatment of arrhythmias in the setting of procainamide toxicity is therefore crucial. Treatment consists of GI decontamination and supportive therapy [66, 67]. Because of potentially slow absorption, emesis or lavage and charcoal should be used even many hours after ingestion. Hypotension, bradyarrhythmias, and seizures are treated with standard measures. Bradyarrhythmias are managed with isoproterenol or pacing (may require higher than usual pacing voltage). Ventricular tachyarrhythmias that cause hemodynamic instability should be treated with lidocaine, phenytoin, bretylium, or overdrive pacing. $NaHCO_3$ or sodium lactate (1 mEq/kg by IV bolus, every 5 – 10 min to achieve an arterial of pH 7.4 – 7.45) may be effective for tachyarrhythmias due to class IA drugs [68]. If associated with hemodynamic stability, sinus tachycardia usually requires no specific therapy. If associated with hypotension or ischemia, but not depressed conduction, sinus tachycardia is treated with propranolol. Mild hypokalemia (3 – 3.5 mEq/L) may be protective, and potassium levels ≥ 3.0 mEq/L may be best treated by close monitoring. For torsades de pointes (polymorphous or atypical ventricular tachycardia), magnesium sulfate (4 g or 40 mL of 10% solution IV as an initial dose) and overdrive pacing with isoproterenol or electricity may be effective [69].

Seizures should be treated with IV administration of diazepam initially and then phenytoin (15 mg/kg IV), at a rate < 50 mg/min.

Patients with persistent hypotension and bradycardia require monitoring of pulmonary arterial pressure. Based on hemodynamic monitoring, unstable patients are treated as follows:

- if low cardiac output (CO) and low pulmonary arterial wedge pressure (PCWP) are present, give more crystalloid fluid;
- if low systemic vascular resistance (SVR) is found give norepinephrine or dopamine;
- if low CO with slow heart rate are present treat with isoproterenol or epinephrine; and
- if low CO and normal or high PCWP occur, use isoproterenol, dobutamine. For intractable cardiogenic shock, cardiac pacing, intra-aortic balloon pump counterpulsation, and cardiopulmonary bypass may be necessary.

Extracorporeal Therapy

Procainamide is extensively distributed to body tissues and is only slightly (15%) protein bound. A relatively small fraction of the total amount of procainamide (V_d = 2.4 L/kg) in the

body is in the vascular compartment, so that extracorporeal removal of the drug is not very effective. In normal persons, the endogenous clearance of the drug is 8.6 – 9.8 mL/kg/min, with a $t^{1/2}$ of about 2.6 – 3.5 hours; in ESRD the clearance is reduced to 4.3 mL/min/kg with a resultant $t^{1/2}$ of 10 – 14 hours. In healthy persons, the clearance of procainamide is not substantially greater than endogenous clearance [68 mL/min by HD 6.4 by PD, and 75 mL/min by HP] [68, 70 – 72]. In contrast, NAPA has a smaller V_d (1.4 L/kg) and minimal protein binding (10%) and a lower endogenous clearance of 3.1 mL/min/kg, so that accelerated drug removal techniques are more useful [65, 71, 72]. Clearance of NAPA by HD is 68 mL/min, with HP 73 mL/min, and with combined HD and HP it increases to 107 mL/min [67]. While the $t^{1/2}$ of procainamide is increased to about 10 hours in ESRD, the $t^{1/2}$ of NAPA (normal 6 hours) is increased to about 36 hours [65].

While the amount of NAPA removed by HP or HD might be a small percentage of the total body burden of the metabolite, potentially fatal dysrhythmias may disappear during these techniques [71, 73 – 76]. Thus a rapid decrease in plasma NAPA during extracorporeal techniques can stabilize cardiac rhythm independently of the total amount removed.

It is important during HD to avoid hypotension. Hypotension can decrease drug clearance due to decreased drug mobilization from tissues into the blood secondary to decreased tissue perfusion [74, 76].

The pharmacokinetics of procainamide and NAPA would suggest that continuous removal would be more efficient. While clearances of NAPA by continuous HD (20 mL/min) [77], continuous arteriovenous hemofiltration (CAVHF) (10 mL/min) [78] and continuous venovenous hemofiltration CVVHF (28 mL/min) [78] are lower than acute HD for 4 hours (54 mL/min) [79], or acute HD plus HP (107 – 117 mL/min) [79] or charcoal HP alone (75 mL/min) [79], the total daily clearances are equal (if not superior) with the continuous techniques (29 – 37 L/day) [77, 78, 80] compared to intermittent therapies (13 – 24 L/day) [79].

Therefore, in conclusion, when the usual routes of drug elimination of procainamide and NAPA are depressed or absent, such as when renal or hepatic failure complicates overdose with these drugs, or when extracorporeal circulation is used to support a failing circulation, HD, HP, or a combination of HD and HP or continuous therapies (CAVHF or CVVHF) should be strongly considered. More specifically, extracorporeal therapy in procainamide toxicity is indicated when:

- serum procainamide concentration are >20 mg/L and either serious cardiovascular or renal failure exist [2];
- combined procainamide and NAPA concentrations are > 60 mg/mL (60 mg/L). This combined level usually is predictive of serious toxicity [65, 67].

Tricyclic Antidepressant Intoxication (TCA)

TCA overdose is the leading cause of hospitalization and death due to excessive ingestion of prescription drugs. Although accidental and intentional exposures to TCAs represented only 1.8% of all poisoning cases reported to the national poison centers during the 1980s, they accounted for 43.8% of all hospital admissions for poisoning, 18% of all poisoning deaths, and for 24% of major morbidity attributed to all sources of drugs or chemicals [81]. Ironically, TCAs remain the most frequently prescribed drugs to treat depressed patients who may be (or may become) suicidal.

Pharmacology and Toxicology

The TCAs are 3-ringed structures resembling phenothiazines. They possess anticholinergic, α-adrenergic blocking, and adrenergic uptake inhibiting properties [82].

The TCAs are rapidly and completely absorbed from the GI tract, with peak plasma concentrations occurring 2 – 8 hours after a therapeutic dose. These agents are metabolized to more polar forms by the liver; the polar metabolites are primarily excreted in the urine. Drug half-life ranges from 24 – 76 hours at therapeutic levels, but may be much longer after an overdose. Other factors that can influence the severity of an overdose include:

– TCAs undergo enterohepatic recirculation, which prolongs the absorption and toxic effects seen in an overdose situation.
– Absorption of TCAs may be considerably delayed in overdose due to their anticholinergic effects.
– The TCAs have a large V_d (10 – 20 L/kg) because they are lipophilic. They are also highly bound to plasma proteins (up to 95% binding at physiologic pH). The combination of a large V_d and protein binding means that forced diuresis, dialysis, and HP have no role in the management of TCA overdose [82, 83].
– Concurrent ingestion of other drugs can affect TCA handling. The catabolism of ethanol, for example, generates an excess of reducing equivalents which diminish the oxidative metabolism of TCAs. Neuroleptics, fluoxetine (Prozac), and toxic hepatic metabolites of acetaminophen also impair TCA metabolism, potentially increasing plasma drug levels.
– Toxic hepatic metabolites of acetaminophen would delay TCA elimination.
– The elderly have slower rates of drug elimination and are particularly susceptible to a TCA overdose.

Clinical Presentation

The presenting signs of a TCA overdose include cardiac arrhythmias, hypotension, and anticholinergic signs (hyperthermia, flushing, dilated pupils, intestinal ileus, urinary retention, and sinus tachycardia) [82, 83, 84 – 86]. CNS involvement is also common. Early signs, such as confusion, delirium, and hallucinations, typically occur before the onset of seizures or coma. The physical examination may reveal clonus, choreoathetosis, hyperactive reflexes, myoclonic jerks, and a positive Babinski sign.

Cardiotoxic effects are responsible for the mortality of TCA overdose. This usually occurs after the ingestion of > 1 g (10 – 20 mg/kg), which can lead to plasma levels > 1000 ng/mL [83]. The most important electrophysiologic action of TCAs is inhibition of the fast sodium channel, leading to slowing of phase 0 depolarization in His-Purkinje tissue and the myocardium [82 – 84]. This toxic effect, which is inhibited by $NaHCO_3$ (see below), slows conduction with resultant QRS prolongation and the potential emergence of reentry arrhythmias (such as ventricular tachycardia, ventricular fibrillation, and torsades de pointes).

As noted above, sinus tachycardia occurs early in TCA overdose when anticholinergic symptoms predominate. In the presence of a wide QRS, however, sinus tachycardia may be difficult to distinguish from ventricular tachycardia.

Hypotension and pulmonary edema are other common findings in TCA overdose. The fall in blood pressure is due both to impaired myocardial contractility and to decreased pe-

ripheral vascular resistance (PVR) induced by α-adrenergic blockade [83, 84, 86, 87]. The decrease in contractility also contributes to pulmonary edema which can be exacerbated by fluid overload. For this reason TCA toxicity must be managed with only maintenance fluid replacement (unless the patient is hypotensive) and preferably with central hemodynamic monitoring in the ICU [82, 83].

Treatment

Treatment of TCA overdose must be aggressive from the outset. Initial therapy consists of establishing airway and breathing, continuous electrocardiographic (ECG) monitoring, gastric lavage, and the administration of activated charcoal [82, 83, 87]. In contrast, syrup of ipecac is contraindicated with any TCA ingestion due to the possibility of rapid neurological deterioration and high incidence of seizures.

Gastric decontamination can be considered for up to 12 hours after ingestion because the anticholinergic properties of these drugs delay gastric emptying. TCAs in the gastrointestinal tract are well absorbed by activated charcoal at a 10:1, charcoal-to-drug ratio. The initial recommended dose of charcoal, 1 – 2 mg/kg body weight, should be given with a cathartic, such as sorbitol or magnesium citrate [87]. This may be followed by an additional 2 – 3 doses at intervals of several hours. These doses can be given with water if catharsis is adequate or with a cathartic if bowel motility is minimal.

$NaHCO_3$

IV $NaHCO_3$ is the single most effective intervention of the management of TCA cardiovascular toxicity [88 – 90]. This agent can reverse QRS prolongation, ventricular arrhythmias, and hypotension. Because acidosis aggravates TCA toxicity, the beneficial action of $NaHCO_3$ may be partly due to correction of acidosis. It is clear, however, that $NaHCO_3$ administration is effective even when the arterial pH is normal. The beneficial effect appears to be mediated by increases in both pH and the plasma sodium concentration ($[Na^+]$) [91]. Alkalinization to an arterial pH of 7.5, for example, appears to reduce the incidence of cardiac arrhythmias, and IV $NaHCO_3$ (in a dose of 1 – 2 mEq/kg) is the treatment of choice for sudden-onset ventricular tachycardia, ventricular fibrillation, or cardiac arrest. To maintain an arterial pH of 7.5, an IV infusion of two 50 mL ampules of $NaHCO_3$ (containing approximately 90 mEq of $NaHCO_3$) in 1 L D_5W is started in all comatose patients, particularly those with a QRS duration > 0.10 sec (100 msec).

Arrhythmias

Lidocaine is the drug of choice for TCA-induced ventricular dysrhythmias. However, care must be taken to avoid precipitation of seizures. In comparison, many antiarrhythmic drugs should not be used with TCA overdoses. Propranolol, for example, depresses myocardial contractility and conduction, while procainamide, disopyramide, and quinidine, via membrane stabilizing effects, may enhance TCA toxicity.

Hypotension

IV fluids are the preferred therapy in hypotensive patients. Dopamine can be used if needed because it has both inotropic and vaso-

constrictor activity. On the other hand, sympathomimetic vasopressor agents carry the risk of precipitating tachyarrhythmias. Levarterenol is generally considered an adjunctive pressor agent [83, 87, 92].

Seizures

Diazepam is the drug of choice in the management of acute-onset seizures. Phenytoin or phenobarbital may be used as second-line drugs.

Physostigmine

Physostigmine, a short-acting cholinesterase inhibitor, has been referred to as the antidote for TCAs because of its ability to increase cholinergic tone and reverse anticholinergic effects. It can, however, cause severe bradycardia, seizures, and asystole by overcompensating for cholinergic tone and suppressing supraventricular and ventricular pacemakers [93, 94]. In the aggregate, physostigine-associated risks often outweigh the benefits. As a result, physostigine should only be used in patients with coma or those with convulsion or arrhythmias resistant to standard therapy.

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Special Issues Related to Pediatric Patients on Dialysis

Charles L. Stewart and Richard N. Fine

Introduction / Overview

The many medical problems that affect patients with end-stage renal disease (ESRD) who require life-maintaining dialytic therapies may have a somewhat different and often very significant impact on the lives of infants, children, and adolescents (compared with adults) with renal failure. Therapy for renal failure in infants and children is often quite challenging considering the infant or child's small size together with the increased metabolic demands of the growing and developing human. The relative physiologic homeostasis that is needed to support the physical and emotional growth and maturation of a child, combined with the complex interpersonal and multidisciplinary interactions required in caring for these patients, suggests the need for a coordinated team of individuals with interest and expertise in the management of children with ESRD. This chapter will address the causes of ESRD in children, the indications for considering dialysis therapies, some of the modifications needed in the institution of chronic peritoneal dialysis (PD) and hemodialysis (HD) in infants and children, including choices of dialysis modalities, differences in dialysis prescriptions, and other issues of medical significance in these children including nutritional considerations, statural growth, and osteodystrophy.

Incidence and Etiologies of ESRD in Children

The spectrum of causes of ESRD in infants and children is somewhat different compared with the causes of ESRD in adults. Recently data regarding the causes of ESRD was reported by The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), a research effort organized and initiated in 1987 originally designed to capture information about practices and trends in immunosuppressive therapy with an ultimate goal of improving the care of pediatric renal transplant recipients [2]. More recently, this cooperative study was expanded to included data on young patients on PD and HD [5] and those with chronic renal failure (CRF) [78]. In the most recent report from this cooperative study [78], when evaluating the causes of ESRD leading to renal transplantation, 3 of the 4 leading causes of CRF were congenital urinary tract disorders (including obstructive uropathy, aplastic/hypoplastic/dysplastic kidneys, and reflux nephropathy). Children with vesicoureteral reflux and some forms of congenital obstructive uropathy may have conditions that are potentially treatable if diagnosed early in life, or diagnosed on prenatal ultrasound. The leading causes of ESRD in the adult age groups, diabetes and hypertension [28], are quite unusual causes of ESRD in

Table 1. Causes of ESRD in Children Resulting in Renal Transplantation

Disease/Condition	Percent
Obstructive uropathy	16.5
Aplastic/hypoplastic/dysplastic kidneys	16.4
Focal segmental glomerulosclerosis	11.6
Reflux nephropathy	5.7
Systemic immunologic disease	4.7
Chronic glomerulonephritis	4.4
Syndrome of agenesis of the abdominal musculature	3.0
Congenital nephrotic syndrome	2.8
Hemolytic uremic syndrome	2.7
Polycystic kidney disease	2.7
Medullary cystic disease/juvenile nephronopthisis	2.6
Cystinosis	2.5
Pyelonephritis/interstitial nephritis	2.3
Membranoproliferative glomerulonephritis type I	2.3
Familial nephritis	2.3
Renal infarct	2.0
Idiopathic crescentic glomerulonephritis	1.8
Membranoproliferative glomerulonephritis type I	1.0
Oxalosis	0.8
Membranous nephropathy	0.6
Wilms tumor	0.6
Drash syndrome	0.5
Sickle cell nephropathy	0.1
Diabetic nephropathy	0.1
Unknown	4.4

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children. Table 1 lists causes of ESRD leading to renal transplantation in children.

Pediatric patients < 20 years of age with treated ESRD (from 1988 – 1992) numbered 4,352 patients, compared with 234,296 total number patients with treated ESRD in the United States from 1988 to 1992 [28]. Table 2 compares the incidence and causes of ESRD in children and adults. It can be noted from this table that while the percentage of adults patients having ESRD from congenital causes is markedly lower than reported in children (0.7 percent in adults compared with 18.5 percent in children), the ages at which these congenital disease cause ESRD in adults are markedly lower than the mean age at onset of ESRD (from all causes) in adults.

Indications for Initiation of Dialysis

Over the past decade, and certainly over the past 5 years, pediatric nephrologists have been judging the need for the initiation of chronic dialysis therapies based on the overall clinical status of the patient, with less reliance

Table 2. Incidence of Treated ESRD in Children and Adults (1988-1992) (Data for adults in parenthesis)

Primary Disease	Total Incidence Count	Percentage of Total	Median Age
All pediatric ESRD	4352 (234,296)	100 (100)	15 (62)
Diabetes	52 (80,834)	1.4 (36.2)	18 (61)
Hypertension	210 (67,239)	5.5 (30.1)	17 (68)
Glomerulonephritis	1387 (28,739)	36 (12.9)	16 (54)
Goodpasture syndrome	20 (719)	0.5 (0.3)	18 (65)
Focal glomerulosclerosis	30 (3,512)	9.1 (1.6)	15 (40)
Membranous nephropathy	23 (1,083)	0.6 (0.5)	15 (56)
Membranoproliferative GN	128 (881)	3.3 (0.4)	15(42)
Other glomerulonephritis	866 (22,544)	22.5 (10.1)	16 (56)
Cystic kidney disease	170 (6,978)	4.4 (3.1)	11 (54)
Interstitial nephritis	169 (7,011)	4.4 (3.1)	16 (63)
Analgesic nephropathy	32 (1,884)	0.8 (0.8)	14 (64)
All other interstitial nephritis	137 (5,127)	3.6 (2.3)	16 (63)
Obstructive uropathy	304 (4,792)	7.9 (2.1)	12 (68)
Collagen vascular diseases	362 (4,982)	9.4 (2.2)	16 (41)
Systemic lupus erythematosus	242 (3,147)	6.3 (1.4)	16 (35)
Scleroderma	NR (546)	NR (0.2)	NR (58)
Wegner's granulomatosis	14 (557)	0.4 (0.2)	16 (63)
Hemolytic uremic syndrome/thrombotic thromboytopenic purpura	67 (483)	1.7 (0.2)	8 (49)
Polyarteritis	NR (127)	NR (0.1)	NR (58)
Henoch-Schonlein purpura	33 (93)	0.9 (0.0)	15 (27)
Rheumatoid arthritis	NR (29)	NR (0.0)	NR (64)
Malignancies	12 (2,962)	0.3 (1.3)	4 (68)
Metabolic diseases	51 (1,143)	1.3 (0.5)	10 (62)
Cystinosis	38 (51)	1 (0.0)	11 (12)
Oxalate nephropathy	13 (89)	0.3 (0.0)	10 (57)
Congenital/other hereditary diseases	710 (1,611)	18.5 (0.7)	11 (22)
Congenital obstructive uropathy	156 (409)	4.1 (0.2)	12 (27)
Renal dysgenesis, agenesis, dysplasia	173 (382)	4.5 (0.2)	9 (22)
Alport syndrome	381(820)	9.9 (0.4)	11 (21)

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on laboratory values representing the degree of renal functional impairment (i.e. blood urea nitrogen (BUN) or serum creatinine levels). In general, with the recent availability of medications to promote the correction of anemia (recombinant human erythopoietin [rHu-EPO]), to ameliorate the significant growth retardation affecting most young children with ESRD (recombinant human growth hormone [rhGH]), and to provide activated vitamin D (calcitriol), the initiation of chronic dialysis often occurs later in children, with levels of serum creatinine somewhat higher than previously encountered at the initiation

of dialysis. As such, there is no particular laboratory value that should be used to justify the initiation of chronic dialytic therapies. Certainly if the child has significant hyperkalemia unresponsive to dietary and pharmacologic therapies, severe acidosis which is unable to be controlled with administration of alkali, uremic pericarditis, or uremic encephalopathy, the need for dialysis becomes clear. In addition, decreased school performance, cognitive development, and psychosocial/behavioral impairment may also prompt the initiation of dialysis and perhaps other therapeutic interventions in children with chronic renal failure [19]. Once it becomes clear to the pediatric nephrologist that dialysis will soon be needed, a decision regarding the method of dialytic therapy will need to be made, and arrangements made for creating either vascular or peritoneal access (or both).

Choice of Dialysis Modality

The decision regarding the methodology of dialysis depends on a number of factors related both to the patient and to the dialysis center's experience and preference. In North America, approximately 66% of persons < 21 years of age with ESRD requiring dialysis were treated with PD, while 34% were treated with HD, in data collected from 1987 through 1992 [4]. However, the relative contribution of PD and HD in the treatment of children with ESRD requiring dialysis varies worldwide on a country to country basis. The European Dialysis and Transplantation Association reported recently that 29% of newly dialyzed children were treated with PD, while 50% of those < 2 years of age were placed on PD [27]. The use of PD as maintenance renal replacement therapy has continued to expand over the past 15 years, and reports suggest that the majority of children (50 – 75%) can be successfully treated with chronic PD for at least several years while awaiting renal transplantation [3].

Despite the recent increase in the use of PD to treat ESRD in children, HD continues to be a viable option in adolescents and older children. Although the technical problems associated with HD in young infants are considerable, this modality in some instances can be successfully used in the infants with ESRD, especially those awaiting transplantation [36,17]. The use of chronically implanted venous catheters or the creation of arteriovenous fistulas in infants and young children have enabled pediatric nephrologists to successfully hemodialyze even very young infants.

Access for Dialysis Procedures

Hemodialysis (HD)

Achieving venous access in infants and young children has been challenging pediatricians, pediatric house officers, and pediatric surgeons for many years. The often very small size of the child, the small size/caliber of their veins and arteries, and, often, the lack of easily visible or palpable veins, together with the knowledge that, in many instances, children develop their renal insufficiency slowly and have required in the past multiple intravenous infusions of fluids or medications with resultant venous injury, scarring and thrombosis, makes the creation and maintenance of ade-

quate access both challenging, frustrating, and rewarding in these young patients.

In infants and children who are to be started on HD as their maintenance dialysis therapy, single and dual-lumen venous catheters, placed either percutaneously or surgically implanted, accounts for vascular access in about half of children on HD, with the remainder divided equally between arteriovenous fistulas and grafts [4]. The site most commonly used for acute vascular access for hemodialysis is the subclavian vein; however, it should be noted that long term or repeated use of the subclavian veins early in life may result in vessel scarring with impaired blood flow from the vein, which may limit the availability of the good venous drainage needed for the future creation of arteriovenous fistulas. The creation of arteriovenous fistulas in small children is an ongoing and often frustrating challenge for the surgeons (who may be vascular surgeons, plastic surgeons, hand surgeons, or pediatric surgeons) involved in the creation of this important source of chronic vascular access; the use of microscopes in the operating room have been used with very acceptable results in small children [63]. With the development and increased usage of tunneled intravenous (IV) access (both percutaneous and surgically placed) for a variety of vascular access needs in infants and young children, this type of access is becoming much more frequently utilized in infants and children requiring acute and chronic HD access [39]. These can be dual lumen catheters in many cases, although single lumen central venous access can be utilized with "single needle" adaptation in the hemodialysis procedure. Despite the increasing use of chronic PD as an initial modality in young children, HD remains an important tool in the treatment of acute and chronic renal failure in infants and children [11, 36].

Peritoneal Dialysis (PD)

The peritoneal access utilized most commonly in children are Tenckhoff curled catheters with single pre-peritoneal cuff-cuff and straight tunnels [80]. Most of these catheters are surgically implanted in the operating room; however, the percutaneous [44, 69] and peritoneoscopic placement [16] in children, while not widely utilized at present, are beginning to be used in children at some centers. When peritoneal catheters are used in young infants, attention should be given to placing the catheter exit site in a position to avoid fecal and urinary contamination [10]; most pediatric nephrologists prefer PD catheters having downward facing exit sites which seems to allow for less accumulation of extraneous material, and less irritation of the exit site area. In some instances, presternal placement of the peritoneal catheter and exit site has been advocated [66]; this may allow less fecal and urinary soiling of the catheter and fewer exit site infections.

Pediatric Dialysis Prescription

Hemodialysis (HD)

The initiation of chronic HD in an infant or young child should of course be performed under carefully controlled circumstances, with close and frequent monitoring of vital signs, blood pressure, physical examination, and assessment of body weight before, during (if available, with in-bed scales) and after HD treatments. With the use of pediatric catheters, small hemodialyzers, and smaller volume blood lines, the extracorporeal blood volume

can often be maintained at < 8 – 10% of the intravascular volume. Blood flow rates generated by the dialysis peristaltic pump usually range from 3 – 5 mL/kg body weight/ minute, often starting at the lower blood flow rate and slowly increasing the rate during the procedure. Heparinization is provided during the HD procedure, typically with a pre-HD infusion of 10 – 20 U/kg/dose with bedside monitoring of the activated clotting time (ACT). The decision on the amount of ultrafiltration (fluid volume to be removed from the patient during the dialysis process) will depend on the extent of the pre-dialysis volume status (including the presence of edema), blood pressure, and the weight gain noted between dialysis procedures [10]. In young infants, careful attention to body temperature during HD is also warranted. The evaluation of hemoglobin, hematocrit, and iron stores is also warranted, since infants may loose a small amount of blood during each dialysis procedure. Monitoring these parameters should be an ongoing process so that the need for adjustments in medications (rHu-EPO and iron) is recognized.

Complications of Pediatric HD

The complications associated with infant and child HD include problems related to vascular access, including thrombosis, stenosis, and infection. Of these, thrombosis is the most common reason for loss of access to the child's circulation. Because of the smaller blood volume in children, hypotension during the HD treatment occurs more commonly than with adults. This requires close monitoring of vital signs, blood pressure, and body weight as well as closer attention to the patient by the HD staff during the treatment. Hypovolemia is often associated with tachycardia, muscle cramping, nausea, and vomiting. Prompt relief of these symptoms is achieved with rapid restoration of circulating volume with normal saline, 5% albumin, or mannitol. Muscle cramping may occur during the HD treatment, and may be related to hypovolemia, hypotension, and electrolyte shifts that may occur during dialysis. Treatments of cramping have included increasing the dialysate sodium concentration, administration of hypertonic saline or glucose during the cramping episode, and the use of oral quinine prior to dialysis if recurrent cramping occurs.

The dialysis dysequilibrium syndrome (DDS) occurs in children, with symptoms often resembling those of hypovolemia. The cause of DDS is not entirely clear, and may relate to the brisk lowering of serum osmolality that occurs during HD, with subsequent development of acute cerebral edema. Manifestations include headache, nausea, vomiting, blurred vision, restlessness and, in severe situations, significant mental status disturbances including disorientation and coma. DDS can usually be avoided by reducing the decrease in osmolality by shortening dialysis time and reducing blood flow rates. In situations where the patient's serum urea nitrogen level is quite high and HD is being initiated, the administration of 0.5 g/kg body weight of mannitol is useful in preventing intracellular fluid accumulation. After several HD treatments, with lowering of the serum urea nitrogen level, this therapeutic intervention is usually no longer needed.

Peritoneal Dialysis (PD)

The PD prescription will need to include the type of dialysis fluid to be instilled, the dex-

trose (or, occasionally, the amino acid) concentration of the instilled fluid, the volume of the instilled fluid, the length of time the dialysis fluid is allowed to dwell within the peritoneal cavity, and the amount of time allowed for drainage of the peritoneal fluid from the peritoneal cavity. Children on continuous ambulatory peritoneal dialysis (CAPD) will usually have commercially pre-filled dialysate "bags" which they will connect to their peritoneal catheter, instill, dwell for 3 – 6 hours, and then drain and instill new dialysate. These children will have a long dwell of dialysate in their peritoneal cavity for 8 to 10 hours overnight. Children on automated PD (APD) will connect (or be connected) to the dialysis infusion tubing at night, with the machine set to deliver, and dwell, a prescribed amount of dialysate. Typically, the nighttime cycles will be every 60 – 120 minutes; at the end of the procedure, before the child is removed from the automated cycler, a daytime dwell is often instilled in the child's peritoneal cavity.

Most of the APD devices currently used will record the amount of dialysate (plus ultrafiltrate) removed during the drainage cycle based on the weight of the drainage bag. The usual amount of dialysis fluid instilled on a chronic basis is 40 – 50 mL/kg body weight (~1100 mL/m^2 body surface area [BSA]) per infusion cycle. After a PD catheter is first inserted, the catheter is not used for several weeks to a month to allow fibrosis around the catheter to avoid dialysate leakage. If this waiting period is possible, the PD catheter should be flushed with very small volumes of heparinized PD fluid to maintain catheter patency and remove residual blood from the insertion procedure. When dialysis is started (whether immediately or after several weeks), low volumes of dialysate are instilled initially (between 10 – 20 mL/kg body weight), with gradually increasing volumes over 1 – 2 weeks, recognizing that the efficacy of dialysis and ultrafiltration will not be optimized until larger volumes of dialysate are used. In patients who need volume removal for the treatment of congestive heart failure, pulmonary edema, effusions, or edema, the use of dialysate solutions with higher dextrose concentrations (4.25% is the highest dextrose concentration commercially available) can be used. A substantial number of infants and children with ESRD requiring dialysis will have significant urine output, and the lower dextrose concentrations can be used (usually, 1.5% dextrose solutions). Often, a higher dextrose concentration solution is used during the longest dwell period (nighttime for patients on CAPD and daytime for those on APD).

Special attention is required for younger infants and children (especially those < 2 years of age) on PD. It has been clinically apparent that neonates and young infants absorb glucose from dialysate more rapidly that older children and adults. Peritoneal equilibration studies have demonstrated that children < 2 years of age transport glucose and creatinine more rapidly than children 3 – 14 years of age, and that children 3 – 14 years of age transport glucose more rapidly than adults [45]. Thus, in order to optimize the dialysis prescription for infants, a balance between shorter dwell times (optimizing ultrafiltration), longer dwell times (optimizing diffusion and thus blood purification) is required [22, 23, 11]. In some instances, the use of the peritoneal equilibration test (PET; modified for children) may assist in formulating an efficient peritoneal dialysis prescription.

Complications of PD

The major complications associated with PD include loss of PD catheter patency due to fibrin deposition or thrombosis withing the

lumen of the PD catheter, occlusion of the PD catheter with the peritoneum preventing inflow or outflow of dialysate (often associated with catheter migration or omental occlusion), and catheter-associated infection. Fibrin deposition or thrombosis is often treatable with the instillation of thrombolytic agents (e.g. urokinase). In addition, catheter infusion or drainage difficulty resulting from catheter migration is occasionally treatable with flouroscopic manipulation of the PD catheter. Infections in PD patients include infections of the catheter skin exit site ("exit site" infections), infections of the PD catheter tunnel, and peritonitis. Data from NAPRTCS show an episode of peritonitis occurring at the rate of one infection every 13.3 months, with the frequency higher in younger children [80].

The host factors involved in the genesis of peritonitis in children have recently been reviewed [12]. Prompt recognition of peritonitis, and prompt treatment, is certainly warranted; decreases in the peritoneal transport of creatinine has been seen using data from PETs in children with peritonitis [50]. Gram-positive organisms are responsible for a significant percentage of peritonitis and exit site/tunnel infections. Exit site infections remain an ongoing issue in the care of PD patients, and may progress to tunnel infections and peritonitis. Caudal positioning of the exit site, the use of chlorhexidine as a cleansing agent [35], and ongoing review of the care and recognition of exit site problems [55] is advisable. Loss of PD catheters due to peritoneal, tunnel, and exit site infections with *Pseudomonas*, *Staphylococcus*, and fungal infections remains a major cause of treatment failure in children on PD. When children on PD require systemic antibiotic therapy, the use of prophylactic oral anti-fungal agents do seem to decrease the subsequent development of fungal peritonitis.

Growth of Children on Dialysis

The impairment of linear growth in children with ESRD treated conservatively or with dialysis and transplantation remains an ongoing therapeutic challenge in both the physical and psychosocial habilitation of infants and children with renal disease. The etiology of growth retardation in children with CRF and ESRD is thought to be multifactorial and includes protein-calorie malnutrition (well described in children with CRF [7, 67], chronic acidosis [75], renal osteodystrophy [29], uremic toxins, and, more recently described, disturbances of the growth hormone (GH)/insulin-like growth factor (IGF) axis [74]. rhGH has been shown in multicentered placebo controlled studies to be effective in treating short children with preterminal CRF on conservative treatment [20]; children on dialysis also increase in height in response to rhGH, although their response tends to be less than those who received rhGH prior to dialysis [82]. After renal transplantation [43], growth is accelerated in growth-delayed children. In transplanted children who are pubertal, rhGH also increased linear growth [30].

The disturbances of the GH/IGF axis in infants and children with growth delay and CRF are currently undergoing active investigation. Plasma GH levels in children are usually normal or high, suggesting GH insensitivity in these children. Plasma GH binding protein concentrations are low in patients with CRF [53]. GH's somatotropic activity is mediated in part by stimulating the production of circulating IGF-1. IGF-1 levels are normal to somewhat decreased in children with CRF. In addition, IGF binding proteins (IGFBPs) are found in the circulation and are present in increased concentrations in children with

CRF. This increased concentration appears to be largely due to impaired renal filtration of low molecular weight proteins [72] and also to increased production of several of the binding proteins [73]. The increase in concentration of circulating IGFBPs will lower free IGF levels. Administration of GH increases IGF-1 levels and IGF bioactivity.

RhGH treatment has been shown to increase the growth velocity and the bone mineral density of children with CRF [37]. In general, children managed conservatively for their CRF respond better to rhGH the younger they are. After transplantation, young age, good allograft function, higher pretreatment growth velocity, and low steroid dose are associated with a better response to rhGH therapy [59]. A recent review of the clinical data suggests that the use of rhGH does not worsen or induce renal osteodystrophy in children with CRF; however, the risk of slipped capital femoral epiphysis and avascular necrosis of the femoral head have been reported in children with renal osteodystrophy and in rhGH-treated children; thus, complaints of bone pain, hip, knee, or gait disturbances should be evaluated aggressively [81]. Although rhGH does induce resistance to the actions of insulin, overt new-onset diabetes mellitus has not developed in children with CRF treated with rhGH [42]. Benign intracranial hypertension has been reported in some children receiving rhGH [40]; thus, regular fundoscopy and attention to headaches and blood pressure is clearly warranted in these children. Finally, the possibility that the increased body mass induced by rhGH may reduce renal function (perhaps by inducing glomerular hyperfiltration) has been examined; over a treatment period of 5 years, creatinine clearance decreased by merely 8 mL/minute/1.73 m^2 [21].

Hyperparathyroidism and Renal Osteodystrophy

Hyperparathyroidism is a well described finding in persons of all ages with CRF. Factors contributing to the development of high parathyroid hormone (PTH) levels in children with CRF include hypocalcemia, hyperphosphatemia, decreased production of activated vitamin D (calcitriol), and decreased clearance of circulating PTH from the circulation. The clinical manifestations of renal osteodystrophy in children may vary depending upon the age of onset of CRF, and includes skeletal deformities, bone pain, growth retardation, extraskeletal calcification, and muscular weakness. The frequency of skeletal deformities in children with CRF is related in part to the normally high rates of bone growth and skeletal remodeling that characterize the growing child. In young children, renal osteodystrophy often resembles vitamin D deficient rickets, with widening of the metaphysis beneath the growth plates of long bones (characterized by enlargement of the wrists and ankles), along with Harrison's grooves and rachitic rosary. Other clinical manifestations of renal osteodystrophy in children are found in Table 3.

Renal osteodystrophy has been shown to represent a spectrum of histopathologic conditions. The most clearly recognized is the "high-turnover" bone lesion osteitis fibrosa. In this lesion, elevated PTH levels result in increases in both osteoclastic and osteoblastic activity, with high rates of bone remodeling, and fibrous tissue found near bone trabeculae, within marrow space, or replacing individual trabeculae [60]. Recently, the prevalence of the "low turnover" bone lesion, termed adynamic or aplastic lesion, has been reported more frequently in the pediatric population.

Table 3. Clinical Manifestations of Renal Osteodystrophy and Secondary Hyperparathyroidism in Children

– Craniotabes
– Frontal bossing
– Enlargement of ankles and wrists
– Rachitic rosary
– Harrison's groove
– Genu valgum
– Slipped epiphyses (femoral)
– Dental abnormalities
– Soft tissue calcification
– Calciphylaxis
– Growth retardation

Osteomalacia is a primary histologic feature, with normal or reduced amounts of osteoid, reduced osteoblastic and osteoclastic activity, no tissue fibrosis, and low or unmeasurable bone formation [61]. Patients may also have histologic evidence of both osteomalacia and osteitis fibrosa, or, mild lesions of renal osteodystrophy, with mild increases in osteoclastic activity and no peritrabecular fibrosis [65].

The treatment modalities available for the prevention and treatment of secondary hyperparathyroidism and renal osteodystrophy in infants and children generally includes attempts to reduce the intestinal absorption of phosphorus (thus reducing hyperphosphatemia) and the administration of various vitamin D sterols. Low-phosphorus diets are generally unpalatable and compliance with this type of diet is quite difficult for children and their families. However, limitation of foods with high phosphorus contents may be somewhat helpful. Most children with CRF will require the use of oral phosphorus binding agents which, when taken with food, reduces intestinal absorption of phosphorus. Aluminum salts, widely used in the recent past, were effective phosphorus binding agents but were found to be associated with aluminum accumulation and resulting osteomalacia and encephalopathy [62, 49, 15]. Recently, calcium salts, most commonly calcium carbonate, have been used as phosphate binders. Liquid preparations of calcium carbonate are available for use in infants and young children unable to swallow tablets. The usual goal of therapy with phosphate binders is to maintain serum phosphorus levels in the mid to upper range of normal levels for age, and to avoid hypophosphatemia.

Several vitamin D sterols have been used to control the high turnover bone lesions of secondary hyperparathyroidism, osteitis fibrosa. The medications currently used include 1,25-dihydroxyvitamin D (calcitriol), dihydroxytachysterol (DHT), and 1-alpha-hydroxyvitamin D (alphacalcidol). A study comparing calcitriol with DHT showed these forms of vitamin D to be equally efficacious in controlling renal bone disease [13]; the cost of DHT is currently substantially lower than calcitriol. Calcitriol may be administered by the oral, intramuscular (IM) [14], IV, or intraperitoneal (IP) route [34]; currently, the only significant advantage to the non-oral forms of therapy with Vitamin D sterols is compliance. Intermittent calcitriol therapy has been found to be effective in reducing PTH levels and healing osteitis fibrosa; intermittent therapy is usually done 2 – 3 times weekly. While many centers are currently using oral calcium salts to bind phosphorus and intermittent oral, IV, or IP calcitriol to control osteitis fibrosa, this combination of therapies has been implicated in the apparently increasing incidence of low turnover adynamic bone disease [25]. Currently, it seems reasonable to maintain a level of intact PTH in a range 2 – 4 times the upper level of normal, and to maintain serum calcium levels within the up-

per ranges of normal. It should be understood that the long-term implications of adynamic bone disease in young children are uncertain.

Anemia

The majority of infants and children with CRF will develop a normochromic, normocytic anemia primarily due to reduced production of erythropoietin (as reflected by reduced serum levels) for the degree of anemia. In addition, other uremic toxins have been implicated in the anemia of CRF [41]. Several of the clinical features of uremia appear to be improved with the use of recombinant human erthyropoietin (rHu-EPO), suggesting that the symptoms may be due in part to the anemia of CRF. These symptoms include fatigue, cognitive dysfunction, cold intolerance, and sleep disturbances [79]. The use of rHu-EPO has been shown to improve cardiac function and exercise tolerance, and also results in subjective improvements in physical performance, health, and school attendance [47, 48]. rHuEPO is not effective in patients with significant iron deficiency [77]. Most children with CRF and anemia will be placed on oral iron therapy in preparation for or during therapy with rHu-EPO. In situations where oral iron administration is not sufficient to achieve iron stores needed for erythropoiesis, IV iron dextran has been used. Children on HD will typically receive rHu-EPO 3 times a week intravenously at the conclusion of their dialysis session, usually beginning with a dose of 50 U/kg body weight per treatment. The subcutaneous administration of rHu-EPO once or twice a week has been shown to be an effective modality for maintaining hemoglobin and hematocrit values in children on PD [46, 57; 68, 51]. In addition, children on PD have been shown to have an effective erythropoiesis receiving rHu-EPO in doses of 100 – 300 units IP given once or twice a week during a long (12 hour) dwell period [58, 70]. The major adverse effects that have been noted in children treated with rHu-EPO has been iron deficiency and hypertension, either exacerbation or de novo. Both of these effects are usually readily managed [32].

Cardiovascular Function and ESRD in Children

Cardiovascular complications of ESRD are not infrequent in children; data from the European Dialysis and Transplant Association have suggested that > 40% of deaths in children < 15 years of age could be attributed to cardiovascular causes [9], with only 17% of the deaths associated with hyperkalemia-induced dysrhythmias. Left ventricular (LV) abnormalities, particularly LV hypertrophy and increased LV mass, have been found in a significant number of children with CRF, patients on PD and HD, and in those children who have had received renal transplants [33]. The causes of these LV abnormalities is probably multifactorial and includes hypertension (a well-known cause of concentric LV hypertrophy), anemia [47], and, possibly, an as yet undefined effect of uremia. [76]. In addition, diastolic dysfunction has been noted in children receiving either PD or HD [26]. Hyperlipidemia has also been found in children receiving either HD [52], PD [56], and those who have undergone renal transplantation [64]. Considering the increasingly long-term survival of infants and children with CRF, assessment of cardiac structure and function by periodic echocardiography, correction of those factors amenable to correction, includ-

ing anemia, hypertension (including the use of home blood pressure and ambulatory blood pressure monitoring), and obesity, as well as on-going studies on the relative risk/benefits of attempts to ameliorate hyperlipidemia, seems prudent.

Nutritional Issues in Infants

Young patients with CRF are at significant risk for protein-calorie malnutrition. Children (especially infants) will often have reduced appetites, gastroesophogeal reflux, vomiting, and delayed gastric emptying, all of which can limit intake of calories and nutrients. Optimal or improved nutrition improves growth [1] and may improve the neurodevelopmental potential in uremic infants [18]. Many children with the onset of ESRD before 2 years of age will require supplemental calories via tube feedings using overnight nasogastric tube feedings or gastrostomy tube placement. However, tube feeding (nasogastric or gastrostomy) may be associated with vomiting and aspiration. Children who start nasogastric tube feedings during the first year of life may also develop feeding dysfunction after the tube feedings have been discontinued, with difficulty noted in chewing and swallowing [71]. Significant protein losses via dialysate in children on peritoneal dialysis have been noted, with losses in infants nearly 2-fold greater compared with older children and adults (when measured as protein losses/m^2 BSA) [55]. The use of amino acid solutions incorporated within the dialysate as the osmotic agent may help to prevent amino acid/protein losses and improve the infant or child's overall nutritional status [6]. Of course assuring the appropriate ingestion of essential vitamins, especially water-soluble vitamins, is required; limiting the intake of the fat-soluble vitamin A may also be required.

Psychosocial Considerations of Dialysis in Infants and Children

CRF and dialysis modalities have a significant and ongoing impact on the psychologic and social well being of children with ESRD and their families. Children will often have major concerns about their physical appearance and the differences between themselves and their peers. Certainly, those with poor growth, episodic edema, Cushingoid facies, external HD or PD catheters, arteriovenous fistulas, and multiple surgical scars may result in features such as low self-esteem, increased anxiety, anger, and behavioral disturbances [24]. In addition, outpatient clinic visits and hospitalizations for illnesses and procedures often require the child to miss school (and the parents to miss work). The response of the parents to the multiple tasks required in the care of these children (including administration of multiple medications, monitoring the child's diet, setting up and performing dialysis for children on home dialysis, or transporting the child for center-based dialysis) can create significant parental relationship problems, anxiety, depression, and parental "burn-out" [38]. Recent reports have suggested that poor adherence to treatment is associated with measures of poor adjustment to diagnoses and dialysis by children and parents, higher self-ratings of anxiety and depression in children and parents, lower family socioeconomic status, and increasing age (younger children had better adherence to therapies than adolescents [8]. Clearly, the availability of psy-

chosocial support of varying types from the dialysis care team is an extremely important process in the therapy for these children and their families.

Conclusions

CRF and ESRD in infants and children remains a major challenge for all of the persons involved in the care of these children. Attempting to adjust the administration of medications and dialysis therapies in order to allow these children to go to school, interact with peers, and achieve as much "normalcy" in their lives as is reasonable, should certainly be a major goal of health care providers and families of these children, while at the same time optimizing the dialysis, medication, and nutritional prescription. In most children, the goal of dialysis therapies is to maintain the patient in as healthy a condition as possible until renal transplantation can be performed.

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Transplantation Immunobiology

Fadi G. Lakkis, Sohail Saleem, Thomas C. Pearson and Christian P. Larsen

Introduction

Transplanting an organ from one member of a species into a nonidentical member of the same species results in a specific immune response referred to as alloimmunity. If left untreated, alloimmune responses lead to rejection of the transplanted organ (the allograft). Rejection of a renal allograft is divided according to histopathologic criteria into hyperacute, acute, and chronic types (Table 1). Hyperacute rejection occurs within minutes to hours after transplantation and is characterized by thrombotic occlusion of the graft vasculature [35]. Acute rejection, on the other hand, occurs within the first few days to few months after transplantation and is characterized by mononuclear cell infiltration of the renal parenchyma and, in severe cases, the vessel walls [76]. Chronic rejection results in allograft loss over the span of months to years. Its histopathologic hallmark is interstitial and glomerular fibrosis [76].

Irrespective of the histopathologic type, rejection is a consequence of the recipient's cellular and humoral immune reaction to non-self antigens in the allograft. This chapter summarizes how non-self antigens (alloantigens) activate the recipient's T lymphocytes, how the resultant alloimmune response leads to rejection, and how this response is regulated. Experimental data relevant to the induction of specific immunologic unresponsiveness to transplanted organs (transplantation tolerance) is also discussed.

The Immunobiology of Allograft Rejection

The immune response to a transplanted organ can be conceptually divided into afferent, efferent (or effector), and regulatory phases (Figure 1). In the afferent phase, host T lymphocytes which recognize alloantigens are activated. These cells then proliferate and differentiate into effector lymphocytes or provide help to other cells which inflict damage on the allograft. Feedback mechanisms which downregulate activated T lymphocytes are essential for keeping immune responses in check and, in certain situations, contribute to long-term allograft acceptance.

The Afferent Phase

The Nature of Alloantigens

The primary non-self antigens responsible for inducing an alloimmune response are the major histocompatibility complex (MHC) molecules, designated as human leukocyte antigens (HLA) in man. HLA are encoded by a family of highly polymorphic genes located

Table 1. Characteristics of Renal Allograft Rejection

	Hyperacute Rejection	Acute Rejection	Chronic Rejection
Onset after transplantation	Minutes to hours (sensitized recipient)	Days to months	Months to years
Pathology	Intravascular thrombi Neutrophilic infiltrates Interstitial edema Cortical infarcts	Mononuclear cell infiltrate involving the tubules and vessel walls	Mononuclear infiltrate Interstitial fibrosis Arteriosclerosis: Intimal myofibroproliferation Glomerulosclerosis
Proposed mechanisms	Preformed anti-HLA or anti-ABO antibodies bind to the vascular endothelium and activate the complement and coagulation cascades	Cellular and humoral immune response to foreign HLA (non-self) present in the allograft	Cellular and humoral immune response to foreign HLA. Non-immunologic factors such as hypertension and reduced renal mass.
Progression to graft failure	Minutes to hours Irreversible	Days to weeks Reversible	Months to years Irreversible

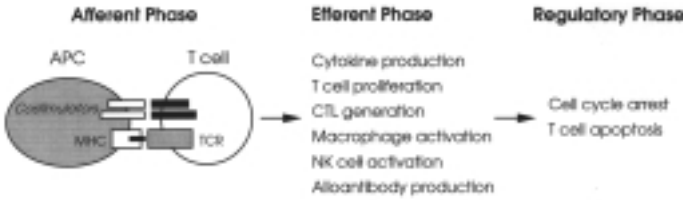

Figure 1. Conceptual phases of the alloimmune response. Abbreviations: APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex; NK, natural killer; TCR, T cell receptor for antigen.

on the short arm of chromosome 6 (Figure 2) [16]. These genes are co-dominantly expressed such that alleles on both chromosomes of a chromosome pair are transcribed and translated into HLA proteins. The total set of alleles present on each chromosome is called a haplotype. An individual, therefore, expresses 2 HLA haplotypes, one inherited from the mother and the other from the father. The highly polymorphic nature of HLA alleles makes it unlikely that 2 unrelated individuals are HLA-identical. In fact, > 150 separate alleles have been identified for certain HLA loci, which makes this gene family the most polymorphic in the human genome. The HLA gene complex also contains genes which code for complement proteins, heat shock protein-70, certain cytokines (tumor necrosis factor and lymphotoxin), and proteins involved in antigen processing, transport, and presentation (Figure 2).

HLA are divided into 2 classes: HLA class I (HLA-A, -B and -C) and HLA class II (HLA-DP, -DQ and -DR) (Figure 2) [16]. Class I proteins are expressed on the vast majority of nucleated cells while class II pro-

Figure 2. Genomic organization of the human major histocompatibility complex. The class II region also contains genes that encode proteins essential for antigen processing, transport, and presentation. Genes that encode tumor necrosis factor, lymphotoxin and heat shock protein-70 are located between the complement and class I regions. The complement region is sometimes referred to as the class III region.

teins are expressed primarily on professional antigen presenting cells (APCs) such as dendritic cells, macrophages, and B lymphocytes. Interferon (IFN)-α, -β and -γ upregulate class I molecule expression in almost all cell types examined [21]. IFN-γ also induces or upregulates class II molecule expression in macrophages, dendritic cells, endothelial cells, and T lymphocytes [52]. On the other hand, interleukin-4 (IL-4) increases class II molecules on B lymphocytes. Class I molecules are composed of a polymorphic transmembrane glycoprotein chain non-covalently associated with β_2-microglobulin [8, 9]. Class II molecules are composed of 2 polymorphic transmembrane glycoprotein chains [15]. The physiologic function of HLA or MHC molecules is to bind antigenic peptides and present them to T lymphocytes [26]. In fact, the T cell receptor for antigen (TCR) does not interact with whole antigens but instead recognizes small antigenic peptides bound to MHC molecules. In general, exogenous antigens (for example, circulating foreign proteins) are taken up by APCs, processed, and presented by class II molecules while endogenous antigens (for example, viral or oncogenic proteins produced within the cell) are presented in the context of class I molecules. The highly polymorphic HLA ensure that humans mount immune responses against a great array of pathogens. Transplantation rejection is therefore the price to be paid for this species survival advantage.

HLA expressed on the cells of an individual are identified by a process known as serologic tissue typing. In this process, antibodies reactive with HLA (alloantibodies) are employed to test for the presence of specific HLA types on the white blood cells of a prospective organ donor or recipient. Alloantibodies were originally derived from the sera of HLA-sensitized donors such as multiparous women, transfusion or transplant recipients, and actively immunized volunteers. HLA identity of a particular individual can also be determined by molecular genetic techniques such as restriction fragment length polymorphism (RFLP). This is especially useful for class II HLA typing [61].

In addition to HLA, polymorphic antigens expressed on donor tissue can induce alloimmune responses. These are referred to as minor histocompatibility antigens which include mitochondrial proteins and sex-related antigens such as H-Y [28, 74]. Although these molecules induce a weaker alloimmune response than HLA, multiple minor histocompatibility differences between the donor and the recipient can lead to rejection of the transplanted organ. This phenomenon could account for rejection observed in recipients of HLA-matched organs. Although ABO blood group antigens were initially thought to be restricted to red blood cells, it is now known that failure to match for these antigens also results in graft rejection, in particular hyperacute rejection [35].

Allorecognition

Recognition of foreign MHC molecules by the recipient's T lymphocytes constitutes the initial event in allograft rejection. Two pathways of allorecognition have been identified:

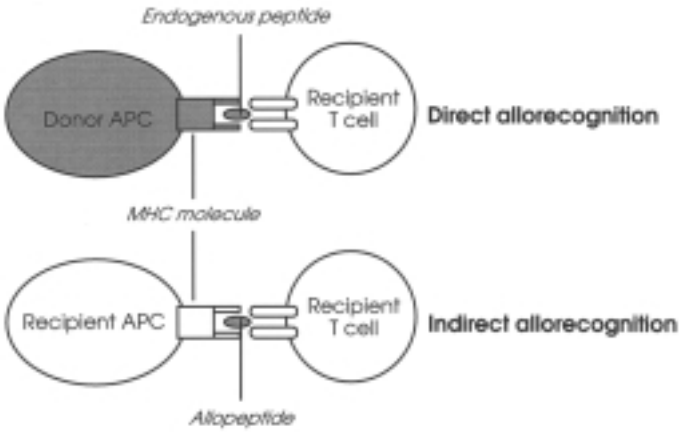

Figure 3. The direct and indirect pathways of allorecognition. In the direct pathway, the recipient's T lymphocytes are triggered by alloantigens expressed on donor APCs. These alloantigens are generally intact allo-MHC molecules (usually class I) complexed to donor endogenous peptides. In the indirect pathway, alloantigens are shed by donor cells, taken up and processed by the recipient's APCs, and presented to the recipient's T lymphocytes in the groove of self-MHC (usually class II).

the direct and indirect pathways (Figure 3) [6, 54]. In the direct pathway, the recipient's T lymphocytes are triggered by alloantigens expressed on donor APCs. These alloantigens are generally intact allo-MHC molecules (usually class I MHC) complexed to donor endogenous peptides. The endogenous peptides may be derived from either major or minor histocompatibility antigens. In the indirect pathway, alloantigens are shed by donor cells, taken up and processed by the recipient's APCs, and presented to the recipient's T lymphocytes in the groove of self-MHC (usually class II MHC). The shed alloantigens could be either major or minor histocompatibility proteins. Antigen processing by APCs requires lysosomal proteases and specialized proteins which ensure that antigenic peptides bind to the appropriate MHC molecule and are transported to the cell surface [26, 27]. HLA-DM is one such specialized protein which facilitates binding of antigenic peptides to the groove of MHC class II . The relative importance of one allorecognition pathway over the other in initiating acute or chronic rejection is currently being studied. It is postulated that the indirect pathway may be particularly important for chronic allograft rejection [54].

Professional APCs play a central role in both allorecognition pathways (Figure 3). As will be discussed later (Section II.A.4), TCR engagement by foreign peptide bound to a MHC molecule is not sufficient for T cell activation and proliferation; a costimulatory signal provided by interactions between molecules on professional APCs with receptors on T lymphocytes is crucial. Professional APCs present in the allograft include mononuclear cells (often referred to as passenger leukocytes), tissue macrophages, and dendritic cells [63]. Ischemia or injury can also induce expression of MHC and costimulatory molecules on non-hematopoeitic cells such as endothelial and renal tubule epithelial cells thus endowing them with APC-like properties [34, 65]. Donor APCs sensitize recipient T lymphocytes within the allograft itself. Alternatively, they may migrate and sensitize recipient T lymphocytes residing in adjacent lymph nodes and the spleen [42, 44]. Histocompatibility antigens shed by the allograft also reach the host's lymphatic organs where they are processed and presented to T lymphocytes by resident APCs. In rodents, depletion of dendritic cells or other APCs from an allograft prior to transplantation prolongs graft survival significantly [45]. This

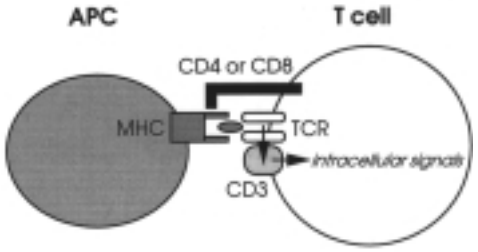

Figure 4. Activation of alloreactive T lymphocytes. The T cell receptor for antigen (TCR) binds to the foreign peptide presented in the groove of self or allo-MHC molecules. The TCR does not directly trigger intracellular signaling but does so through non-covalent interactions with the CD3 complex. CD4 and CD8 function as co-receptors which enhance T lymphocyte activation by binding to non-polymorphic regions of MHC class II and class I molecules, respectively.

approach may be less helpful in clinical transplantation because human endothelial cells constitutively express HLA and costimulatory molecules and activate alloreactive T cells in the absence of dendritic cells or passenger leukocytes [65].

Activation of Alloreactive T Lymphocytes

The response of a T cell population to allostimulation is very potent and involves both CD4+ and CD8+ T lymphocytes. The potency of the alloimmune response is in part due to the high frequency of human T lymphocytes which recognize alloantigen (alloreactive). The first event in alloreactive T lymphocyte stimulation occurs when its TCR binds the foreign peptide presented in the groove of self or allo-MHC molecules. TCRs on the majority of T lymphocytes are composed of 2 disulfide-linked polymorphic chains (α and β) which confer antigen specificity (Figure 4) [17]. The α and β chains do not directly trigger intracellular signaling pathways but do so through non-covalent interactions with other members of the TCR complex, mainly the CD3 molecule (Figure 4) [17]. The intracellular signaling machinery involved in T cell activation includes protein tyrosine kinases (*Src*, *lck*, *fyn*, and ZAP-70), phospholipases ($PLC\gamma_1$), and calcium-dependent protein phosphatases (calcineurin). These signaling pathways ultimately lead to the nucleus where events associated with cell proliferation are initiated and cytokine/cytokine receptor gene transcription is induced. Among the early nuclear events are induction of the *c-fos* and *c-jun* transcription factors. The immunosuppressive agents cyclosporine and tacrolimus (FK506) bind to cytoplasmic proteins called immunophilins (cyclophilin and FK binding protein) [22]. These complexes then block T cell activation by binding to calcineurin and inhibiting its functions.

CD4 and CD8 function as co-receptors which enhance T lymphocyte activation (Figure 4) [56]. CD4 and CD8 bind to non-polymorphic regions of MHC class II and class I molecules, respectively. This interaction brings the cytosolic domains of CD4 and CD8 in proximity of the TCR where they contribute to triggering essential intracellular signaling pathways. Binding of CD4 or CD8 to MHC molecules also strengthens the TCR-MHC interaction and increases the efficiency of T lymphocyte activation.

Costimulation of Alloreactive T Lymphocytes

Engagement of the TCR complex with alloantigen is necessary but not sufficient for inducing T lymphocyte proliferation and subsequently, differentiation into effector cells. The second activation signal is provided by costimulatory molecules on the surface of professional APCs which bind to specific receptors on the surface of T lymphocytes (Fig-

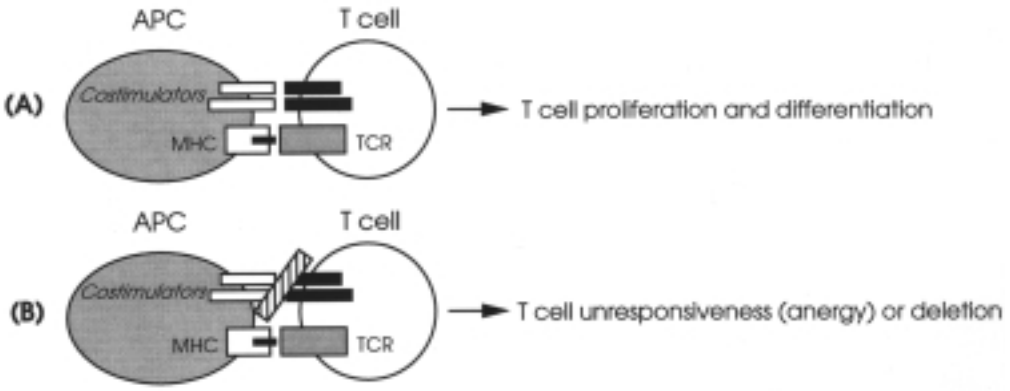

Figure 5. The importance of T cell costimulation. Engagement of the TCR complex with alloantigen induces T lymphocyte proliferation only when coupled with a second activation signal provided by costimulatory molecules on the surface of APCs. TCR engagement in the absence of costimulation may lead to deletion of or anergy in the responding T cell population.

ure 5) [70]. In fact, TCR engagement in the absence of costimulation may lead to deletion of or anergy in the responding T cell population (Figure 5). This phenomenon has been exploited to induce transplantation tolerance in experimental animals.

Among the best studied costimulatory molecules are the B7 family of proteins and the CD40 molecule (Figure 5). The B7 family includes at least 2 members: B7-1 (CD80) and B7-2 (CD86) [48]. B7-1 and B7-2 are homologous transmembrane glycoproteins expressed on professional APCs such as dendritic cells, macrophages, and activated B lymphocytes. Their expression is upregulated by cytokines produced during tissue inflammation; for example, granulocyte macrophage colony stimulating factor (GM-CSF) and IFNγ. B7-1 and B7-2 bind to CD28 on the surface of T lymphocytes. CD28 cross-linking facilitates T cell activation by at least 2 mechanisms. First, CD28-mediated signals increase the expression of cytokine genes, including the T cell autocrine growth factor IL-2. Second, CD28 cross-linking increases expression of Bcl-xL, an intracellular protein which protects resting T lymphocytes against programmed cell death (apoptosis). That the B7-CD28 costimulatory pathway is critical for allograft rejection is demonstrated by studies showing markedly prolonged allograft survival in experimental animals treated with CTLA4Ig, a recombinant protein which binds B7-1 and B7-2 with high affinity and prevents their interaction with CD28 [70].

Like B7-1 and B7-2, CD40 is a glycoprotein expressed on the surface of professional APCs and endothelial cells [25]. CD40 binds to CD40 ligand (CD40L or gp39) on activated T lymphocytes. The discovery that hyper-IgM syndrome is caused by a disruptive mutation in the CD40L gene provided direct evidence that CD40-CD40L interactions play a critical role in humoral immunity. Patients with this syndrome are profoundly deficient in generating CD4+ T cell-dependent antibody responses and antibody isotype switching. CD40-CD40L interactions also promote T lymphocyte proliferation and clonal expansion. This occurs because CD40L cross-linking delivers a costimulatory signal to T lymphocytes or because CD40L-CD40 interactions upregulate B7 expression on APCs which in turn activate T cells. That the CD40-

CD40L costimulatory pathway plays a crucial role in allograft rejection is demonstrated by studies showing significantly prolonged allograft survival in experimental animals treated with monoclonal antibodies to CD40L [43]. Importantly, combined blockade of the B7-CD28 and CD40-CD40L costimulatory pathways leads to long-term allograft acceptance and, in some situations, transplantation tolerance [40]. This therapeutic strategy is currently being tested in non-human primates.

Other APC membrane molecules that may act as costimulators include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and leukocyte function-associated antigen-3 (LFA-3) which bind to very late activation antigen-4 (VLA-4), LFA-1, and CD2 (also called LFA-2) on T lymphocytes, respectively [30, 70). Blocking interactions between these ligand pairs prolongs experimental allograft survival to variable degrees [31]. CD45 (leukocyte common antigen) is a T cell surface protein required for optimal T cell activation [87]. Its cytosolic domain contains intrinsic protein phosphatase activity which dephosphorylates critical tyrosine residues on protein kinases involved in TCR-mediated intracellular signaling thus potentiating T lymphocyte activation. Inhibiting the CD45 signaling pathway delays allograft rejection in rodents. The physiologic ligand for CD45 has not been identified.

Adhesion Molecules and Chemokines

Successful initiation of alloimmune responses requires migration of APCs from the allograft to the recipient's lymphoid organs, infiltration of the allograft with recipient's APCs and lymphocytes, and stable conjugation of APCs to alloreactive T lymphocytes. These functions are orchestrated by adhesion molecules and by chemokines (chemoattractant cytokines).

Migration of leukocytes across endothelial barriers is initiated by the selectin family of adhesion molecules [78]. Interaction between L-selectin on leukocytes and E-and P-selectin on activated endothelial cells allows neutrophils, monocytes, and unprimed (naive) lymphocytes to attach to the endothelium of inflamed tissues. Organs which have gone through an ischemia/reperfusion period exhibit upregulated expression of E-and P-selectins on their endothelium [85]. Selectin-mediated leukocyte-endothelial cell interactions, however, are weak and are insufficient for migration of leukocyes into the allograft. Strong adhesion of leukocytes to the endothelium is mediated by integrins. Integrins are membrane proteins whose expression on circulating neutrophils, monocytes, and lymphocytes is triggered by chemokines present in high concentrations at the site of inflammation [30]. In fact, chemokines are concentrated at the inflammatory site by binding to proteoglycans on the endothelium. Chemokines involved in leukocyte recruitment are produced by activated macrophages, endothelial cells, interstitial fibroblasts, and platelets [5, 71]. Integrins which mediate naive T lymphocyte migration across endothelial barriers include LFA-1 and VLA-4. LFA-1 binds to ICAM-1 and ICAM-2 while VLA-4 binds to VCAM-1 on endothelial cells. Other members of the VLA group of integrins play a role in retaining infiltrating T lymphocytes in the inflammatory site by binding to extracellular matrix proteins such as fibronectin, laminin, and collagen [30].

In addition to their role in leukocyte migration, adhesion molecules facilitate T lymphocyte activation by securing strong association between APCs and alloreactive T cells. This association is mediated in part by LFA-

1/ICAM-1 and CD2/LFA-3 interactions [30, 70]. As discussed previously, LFA-1 and CD2 also transduce costimulatory signals to T lymphocytes.

The Efferent Phase

Once activated, alloreactive T lymphocytes proliferate and differentiate into effector lymphocytes or provide help to other cells which inflict damage on the allograft. The majority of helper T lymphocytes (Th) are of the CD4 phenotype (CD4+) while effector T lymphocytes, such as cytotoxic T lymphocytes (CTL), are mainly CD8+. Other mediators of allograft rejection include mononuclear phagocytes, natural killer (NK) cells, and B lymphocytes which produce alloantibodies. It is important to emphasize that allograft rejection is the end-result of multiple effector pathways proceeding in parallel or overlapping fashions.

Helper T Lymphocytes and their Cytokine Products

An important function of activated CD4+ Th lymphocytes is to secrete cytokines which amplify and *regulate* the immune response. Cytokines exert their actions in an autocrine or paracrine fashion [1, 62]. Although they have been extensively studied in vitro, their in vivo functions are more complex than expected because of redundancy, pleiotropism, and the fact that a single cytokine may have multiple effects on the same target cell.

IL-2 and IFNγ are Th-derived cytokines produced within the first few hours of an immune response [11, 75]. IL-2 is a potent T lymphocyte mitogen which promotes CTL generation and NK cell activation in vitro. IFNγ upregulates MHC expression on APCs and stimulates macrophages and CTLs. It also induces B lymphocytes to produce antibody isotypes which bind complement. Based on their in vitro actions, it is inferred that IL-2 and IFNγ are crucial mediators of allograft rejection. Recent studies in cytokine gene-knockout mice, however, have raised doubts about this assumption [29, 84]. First, vigorous acute rejection occurs unimpeded in mice which lack IL-2, IFNγ, or both [68, 80]. Second, CTL generation is not impaired in IL-2 gene-knockout mice and is, in fact, enhanced, in IFNγ gene-knockout mice [20, 36, 80]. Third, alloantigen-driven T lymphocyte proliferation is augmented, rather than reduced, in the absence of either IL-2 or IFNγ [20, 36, 84]. Fourth, endogenous IL-2 and IFNγ may contribute to induction of long term allograft acceptance under certain experimental conditions [19, 36]. These findings underscore the redundancy of cytokine actions in vivo and the possibility that cytokines considered to be pro-inflammatory also have essential regulatory roles. Other pro-inflammatory cytokines produced by Th lymphocytes include lymphotoxin (LT) [1]. Like TNF, LT activates macrophages and endothelial cells to produce mediators of tissue injury. The contribution of LT to acute or chronic allograft rejection is not known.

Th lymphocytes also secrete cytokines with anti-inflammatory properties. These cytokines include IL-4, IL-10, and IL-13 which possibly derive from a distinct subset of Th lymphocytes referred to as Th2 in mice [4]. IL-4, IL-10 and IL-13 are potent suppressors of macrophage functions. IL-4 also inhibits the differentiation of naive T lymphocytes into IL-2, IFNγ, and LT-producing Th lymphocytes (referred to as Th1 lymphocytes in mice). The functional dichotomy of Th cells led many investigators to propose that preponderance of Th2 cytokines may facilitate long

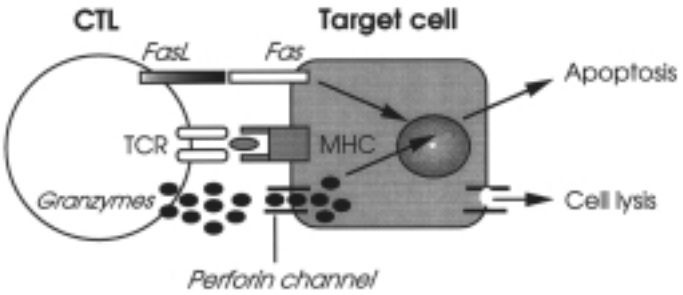

Figure 6. Mechanisms of target cell killing by cytotoxic T lymphocytes (CTL). CTLs recognize target cells in an alloantigen-specific manner. Perforin channels lead to cell lysis while granzymes and Fas-mediated signals lead to cell apoptosis.

term allograft acceptance. Rodent experiments, however, have yielded conflicting results. Mounting evidence suggests that long term allograft survival is not dependent on the presence of IL-4 [39, 60], and that IL-4 overexpression does not lead to allograft acceptance [58, 83]. Moreover, IL-10 enhances CTL activity and its administration to mice can accelerate rejection [97]. The redundancy and complexity of cytokine actions in vivo make it less likely that cytokine-targeted therapies will have significant utility in clinical transplantation.

Cytotoxic T Lymphocytes

CTLs play an important role in allograft rejection by lysing target cells which bear MHC-associated antigens [32, 50]. The majority of CTLs express CD8 molecules and recognize foreign MHC class I molecules. Occasional CTLs are CD4+ and recognize foreign MHC class II molecules. CTLs develop from precursor T lymphocytes (pre-CTL) activated by the foreign antigen, costimulator molecules on professional APCs, and cytokines such as IL-2 and IL-12. Upon contact with target cells, CTLs bring about their death by at least 2 pathways (Figure 6). One pathway is mediated by release of granules containing membrane pore-forming proteins called perforins, and a family of proteases called granzymes. Perforins form large pores in the cell membrane and cause osmotic lysis while granzymes enter the cytosol through perforin channels and induce cell death by apoptosis. The second pathway is mediated by binding of Fas ligand (FasL) on activated CTLs to the Fas receptor on target cells. Fas belongs to a family of "death receptors" which signal cell apoptosis [59]. Disruption of either peforin or Fas pathways does not abrogate allograft rejection suggesting that these mechanisms are redundant [41, 72]. It appears that rejection of MHC class I-disparate grafts is dependent on CTL activity while rejection of MHC class II-disparate or fully allogeneic grafts is not [77]. This underscores the importance of other effector mechanisms such as those mediated by CD4+ T lymphocytes, macrophages, NK cells, and B lymphocytes.

Mononuclear Phagocytes or Macrophages

In addition to their role as APCs, monocytes which infiltrate organ transplants and differentiate into macrophages may contribute to the rejection process. Macrophages are central effectors in delayed-type hypersensitivity (DTH) reactions [2]. Upon activation with IFNγ or LT secreted by CD4+ T lymphocytes, they release a host of tissue injury mediators.

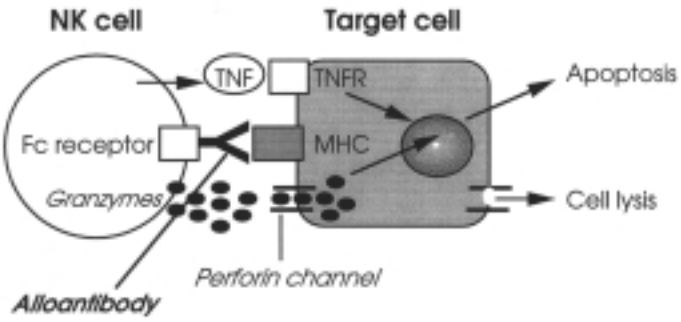

Figure 7. Mechanisms of target cell killing by natural killer (NK) cells. NK cells recognize target cells coated by alloantibodies and lead to their death by lysis or apoptosis. This form of cell killing is known as antibody-dependent cell-mediated cytoxicity (ADCC).

These include cytokines (TNF, IL-1, IL-6, IL-10, IL-12, and IL-15), chemokines, reactive oxygen species, nitric oxide, proteolytic enzymes, and extracellular matrix proteins that lead to fibrosis. TNF induces expression of adhesion molecules on endothelial cells, enhances intravascular thrombosis, and activates neutrophils, eosinophils, and macrophages [7]. Like TNF, IL-1 mediates local tissue inflammation [23]. Although IL-1 was initially thought to be an important T cell costimulator, there is little in vivo evidence to support this hypothesis. IL-6 stimulates growth of activated B lymphocytes at a late stage in their differentiation into plasma cells [1]. IL-12 induces IFNγ production by NK and T cells and enhances their cytolytic functions [86]. IL-12 also promotes differentiation of murine CD4+ T cells into the Th1 phenotype. IL-15 is structurally homologous to IL-2 and serves as a mitogen to NK and T cells [1]. Nitric oxide (NO) is a potent vasodilator. NO production has beed detected during acute allograft rejection, but its role in this process is not understood because it has both pro-inflammatory and anti-inflammatory or immunosuppressive effects [53].

Natural Killer Cells

NK cells are a lymphocyte subset which expresses neither T nor B lymphocyte markers [2]. Because of their relatively large size and their granule-rich cytosols, they are often referred to as large granular lymphocytes. NK cells are activated by IL-2, IL-15 and IFNα. Like CTLs, NK cells kill target cells by releasing perforins and granzymes (Figure 7). In addition, they secrete tumor necrosis factor (TNF) which can induce cell apoptosis. Unlike CTLs, NK cells lack antigen-specific receptors. They express a low affinity receptor for the constant (Fc) portion of IgG thereby binding to and killing antibody-coated target cells (antibody-dependent cell-mediated cytotoxicity or ADCC) (Figure 7). More recently, receptors which recognize MHC class I molecules complexed to self peptides have been discovered on human NK cells [57]. Many of these receptors are inhibitory such that NK cells are shut down when they engage self MHC proteins. This implies that NK cells react to non-self by recognizing the absence of self peptides in the grooves of MHC class I molecules [33].

The contribution of NK cells to allograft rejection is not known. Although NK cells infiltrate solid organ transplants, NK cell depletion does not significantly alter acute rejection [14]. Recent experimental data, however, suggest that NK cells may be involved in delayed allograft loss similar to that seen in patients with chronic rejection (unpublished data).

B Lymphocytes and Alloantibodies

Production of MHC-specific antibodies (alloantibodies) is a T cell-dependent process which requires cooperation between APCs, T lymphocytes, and B lymphocytes. Interactions between CD40 on activated B lymphocytes and CD40L on activated T lymphocytes play a central role in antibody production and isotype switching. Alloantibodies cause tissue damage by activating the complement cascade or by mediating ADCC. The latter occurs when NK cells or macrophages bind to the Fc region of antibody molecules and induce lysis of target cells (Figure 7) [2]. The most dramatic example of antibody-mediated allograft damage is hyperacute rejection. This form of rejection is initiated by pre-formed donor-specific alloantibodies which bind to antigens on the graft's vascular endothelium. Subsequently, complement and coagulation cascades are activated leading to wide-spread endothelial damage and intravascular thrombosis. Pre-formed antibodies which cause hyperacute rejection include anti-ABO and anti-HLA IgG antibodies, particularly those targeted against class I HLA (positive T cell crossmatch) [94]. The latter are found in recipients who have history of previous transplants, multiple transfusions, or pregnancies. Hyperacute rejection has been largely eliminated by routine cross-matching performed immediately before transplantation. Alloantibodies also contribute to acute and chronic rejection but their relative importance is not known. B cell-deficient mice, for example, are capable of vigorous acute allograft rejection. Chronic transplant arteriosclerosis, however, does not develop in B cell-deficient mice suggesting that alloantibodies play an important role in chronic rejection [67].

The Regulatory Phase

A cardinal feature of all immune responses is that they are self-limited. Elimination of the antigen which triggered lymphocyte stimulation in the first place is the ultimate means by which immune responses are terminated. Several downregulatory mechanisms, however, come into play even at early stages of the immune response and are especially important in modulating responses to large or persistent antigen loads such as transplanted organs. These mechanisms include cell surface molecules and cytokines which regulate proliferation and survival of activated T lymphocytes.

Factors that Regulate T Cell Proliferation

Experimental evidence suggests that CTLA-4 molecules expressed on the surface of activated T lymphocytes deliver downregulatory signals which arrest cell proliferation [38, 91, 92]. CTLA-4 stands for cytotoxic T lymphocyte antigen-4 which was originally described in CTLs. CTLA-4 is expressed in low numbers on all resting T lymphocytes and is significantly upregulated within 24 to 72 hours after their activation [49]. The natural ligands of CTLA-4 are the B7 family of costimulatory molecules present on APCs. In fact, B7 proteins bind to CTLA-4 with much higher affinity than their binding to CD28. Unlike CD28, however, CTLA-4 engagement leads to cell cycle inhibition [38, 91]. Gene-knockout mice deficient in CTLA-4 expression exhibit massive accumulation of proliferating lymphocytes in lymphoid and non-lymphoid organs [93]. Furthermore, induction of tolerance to a protein antigen is dependent on CTLA4 engagement by APCs [64]. Although these observations indicate that CTLA4 limits immune responses in vivo,

other data suggest that CTLA4 may have costimulatory functions in vitro [51].

Although IL-2 is a potent mitogen to resting T lymphocytes, it programs these cells to proceed through a limited number of proliferation cycles and to undergo apoptosis when restimulated with antigen. Gene-knockout mice that do not produce IL-2 or those that lack functional high affinity IL-2 receptors develop lymphoid hyperplasia and severe autoimmunity when exposed to normal bacterial flora [29, 84]. T cells activated in vitro or in vivo in the absence of IL-2 are resistant to apoptosis induced by antigenic rechallenge [47]. The latter phenomenon is referred to as activation-induced cell death and constitutes an important immunoregulatory mechanism. Taken together, these findings suggest that IL-2 plays a dual role in the immune system. On one hand, it has a redundant mitogenic role that can be replaced by other lymphocyte growth factors such as IL-4, IL-7, IL-9 and IL-15. On the other hand, it is critical for limiting immune responses.

Like IL-2, IFNγ has dual functions. It effectively induces MHC class II molecule expression and activates macrophages. On the other hand, it limits proliferation of activated T lymphocytes. Gene-knockout mice deficient in IFNγ expression display exaggerated T lymphocyte proliferation and CTL generation upon allostimulation [20, 36]. In rodents, IFNγ is not required for acute allograft rejection but, instead, is essential for induction of long-term vascularized allograft survival [36]. Unlike IL-2, IFNγ does not appear to influence survival of activated T lymphocytes (unpublished data).

Factors that Regulate T Cell Survival

Repeated stimulation of T lymphocytes by antigen may result in apoptosis of the activated T cells instead of continued proliferation. This phenomenon is known as activation-induced cell death (AICD) [3, 88]. AICD may be particularly crucial for controlling immune responses to persistent self-antigens or alloantigens. AICD is in large part mediated by interaction between the cell surface molecule Fas (CD95), a “death” receptor, and its ligand (FasL) [89]. Antigenic stimulation upregulates Fas expression and induces de novo FasL expression on T lymphocytes. FasL-Fas binding then leads to apoptosis of activated T lymphocytes. Other membrane molecules which trigger T cell apoptosis include the TNF receptor (TNFR) and CD30. It is proposed that FasL-Fas pathway mediates AICD of most CD4+ T lymphocytes while TNF-TNFR interactions mediate AICD of most CD8+ T cells [97]. Evidence that Fas and FasL play an important immunoregulatory role in vivo derives from mice which lack functional Fas or FasL proteins. These mice, known as *lpr* and *gld*, respectively, exhibit significant lymphadenopathy and develop an autoimmune disorder which resembles human systemic lupus erythematosus [24]. Furthermore, immune privilege in certain organs such as the eye is partially mediated by heightened FasL expression. Enthusiasm that FasL overexpression on an allograft may lead to long term acceptance, however, has been tempered by experimental data showing that this strategy does not necessarily delay acute rejection in rodents. T lymphocyte survival is also regulated by intracellular proteins induced following antigen recognition and costimulation. These include bcl-xL, which enhances T cell survival [12, 13].

As discussed previously, IL-2 programs activated T lymphocytes to undergo apoptosis upon restimulation with antigen [47, 90]. High concentrations of IL-2 have been shown to upregulate Fas expression and to sensitize T lymphocytes to Fas-mediated apoptosis [90].

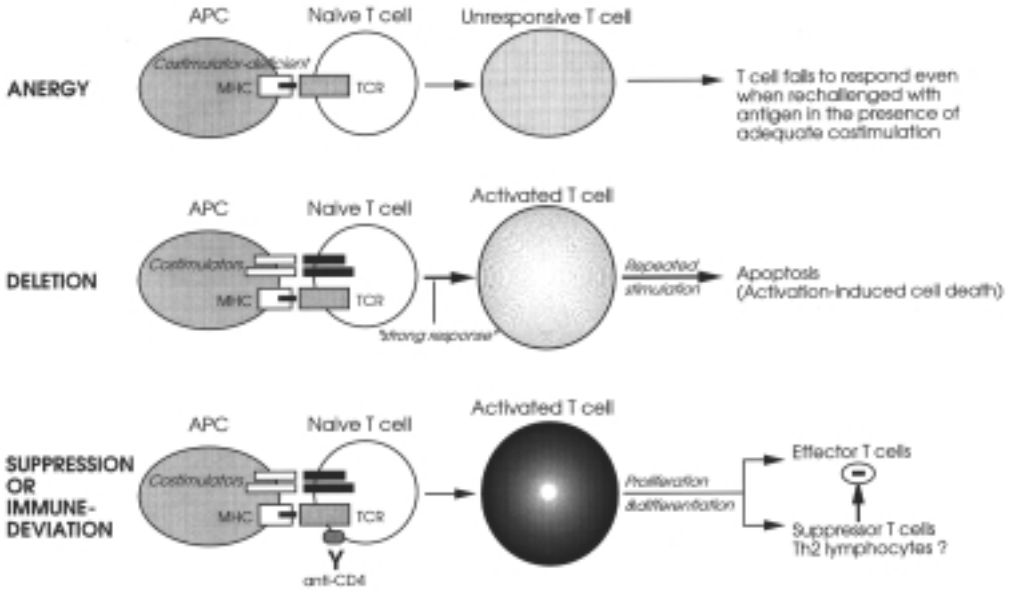

Figure 8. Mechanisms of transplantation tolerance.

These homeostatic actions of IL-2, however, are not necessarily limited to the Fas pathway.

The Immunobiology of Transplantation Tolerance

Transplantation tolerance can be defined as indefinite allograft survival in the absence of continuous immunosuppressive treatment. Implicit to this definition is that tolerant recipients are unresponsive to donor antigens while maintaining reactivity to other antigens. In the clinical setting, a tolerant individual is someone who can mount an effective immune response against vaccines or pathogens but is incapable of rejecting the transplanted organ. Except for the rare patient who stops immunosuppression and maintains a functioning renal allograft, clinical tolerance has not been achieved yet.

Tolerance in experimental animals has been traditionally divided into 2 forms: central and peripheral. Central tolerance occurs in the thymus where self-reactive T cells are deleted. Peripheral tolerance, on the other hand, occurs extrathymically and is crucial for achieving unresponsiveness to foreign antigens in the adult animal in whom the thymus has involuted. Proposed mechanisms of peripheral transplantation tolerance include anergy, deletion, suppressor T cells, and immune deviation of alloreactive T lymphocytes from a "destructive" Th1 to a "protective" Th2 phenotype (Figure 8) [18, 37, 46]. These mechanisms are not mutually exclusive.

Anergy and Deletion

Anergy is defined as functional inactivation of antigen-specific T cells in the absence of cell death [66, 73]. Deletion, on the other hand, results from apoptosis of the antigen-

specific T cell clone [18, 37, 46]. It is not known whether anergy and deletion represent different stages of a continuum of lymphocyte inactivation, or whether they result from distinct tolerogenic signals. The former possibility is supported by experiments showing that the same tolerance-induction strategy often leads to both anergy and deletion in the alloreactive T cell population.

At least 2 pathways may lead to anergy and/or deletion of T lymphocytes in vitro and in vivo. First, T cells activated by antigen in the absence of costimulatory signals are rendered anergic or are deleted, suggesting that compromised antigen presentation results in tolerance (Figure 8). This has been achieved in mice by agents that block the B7-CD28 and CD40-CD40L T cell costimulation pathways. Alternatively, tolerance can be achieved by infusing a large number of donor white blood cells (obtained from the donor's circulation, spleen, or bone marrow) intravenously prior to transplantation. It is proposed that the intravenous route of antigen administration is tolerogenic because it does not recruit professional APCs which express an abundance of costimulatory molecules [55]. Second, T cells repeatedly challenged by antigen in the presence of adequate costimulation can also become anergic or are deleted, suggesting that overstimulation results in tolerance (Figure 8) [37]. This phenomenon probably accounts for spontaneous acceptance of liver allografts in mice. Pre-clinical studies are currently under way to test the effectiveness of costimulation blockade, donor-specific bone marrow infusion, or both in inducing tolerance to renal allografts in non-human primates.

Suppressor T Cells and Immune Deviation

An individual may also develop tolerance to the donor's antigens despite the presence of responsive, alloreactive T lymphocytes (Figure 8). Two mechanisms have been proposed to account for this situation. Proliferation and differentiation of alloreactive T lymphocytes may be inhibited by antigen-specific suppressor cells. Alternatively, T lymphocytes proliferate in response to alloantigen but differentiate into a non-harmful phenotype (immune deviation). Although it has been repeatedly shown that T cells from a tolerant animal can adoptively transfer antigen-specific unresponsiveness to a naive animal, it has been extremely difficult to isolate and study suppressor T cells [10]. It is postulated that suppressor T cells function in an antigen-specific fashion by secreting soluble TCRs which bind to MHC-associated antigens on APCs and competitively inhibit activation of other T lymphocytes. Suppressor T cells may also secrete immunosuppressive cytokines such as transforming growth factor-β (TGFβ).

The immune deviation hypothesis has lately emerged as an alternative to suppressor T cells. Implicit to this hypothesis is the existence of 2 distinct and reciprocally-regulated Th lymphocyte subsets [4]. Th1 lymphocytes secrete IL-2, IFNγ, and LT. Th2 cells, on the other hand, secrete IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. Both cell types originate from the same precursor lymphocyte (Th0) and their differentiation is largely influence by cytokines present at time of antigen recognition. The presence of IL-12 and IFNγ favor the Th1 phenotype while IL-4 promotes generation of Th2 lymphocytes. Th1-derived cytokines are considered to promote rejection by mediating DTH reactions, CTL generation, macrophage activation and production of complement fixing antibodies. In contrast, Th2-derived cytokines are proposed to protect against rejection by suppressing DTH reactions and counteracting IFNγ's actions on macrophages. They also deviate antibody production towards IgE and non-complement fixing subclasses of IgG. Th1 and Th2 subsets

are reciprocally regulated. IFNγ inhibits the differentiation and proliferation of Th2 cells resulting in a dominant Th1 response. On the other hand, IL-4 and IL-10 inhibit IFNγ production by Th1 lymphocytes. A direct correlation between Th2 cytokine expression and long term allograft acceptance has been observed in experimental animals [69, 82]. Furthermore, a causal relationship between IL-4 production and transplantation tolerance induced by neonatal infusion of donor cells or by administration of non-depleting anti-CD4 antibodies is suggested by some rodent studies [81]. Tolerance achieved by T cell costimulation blockade, however, is not dependent on IL-4 [39, 60], and IL-4 overexpression in allografts does not significantly delay rejection [58, 83]. In fact, induction of tolerance or long term allograft survival in certain experimental models is facilitated by endogenous production of Th1 cytokines (IL-2 and IFNγ) [19, 36, 90]. The pertinence of the immune deviation hypothesis to clinical transplantation is further questioned by the uncertainty whether Th1 and Th2 subpopulations exist in humans.

Other Pathways that Lead to Transplantation Tolerance

Induction of antigen-specific unresponsiveness by administering peptides derived from HLA have shed novel insight into tolerance mechanisms [54]. Peptides derived from non-polymorphic regions of HLA exert their immunosuppressive effects by blocking CD8-MHC class I interactions or CD4-MHC class II interactions. Alternatively, they can bind to heat shock proteins and modulate intracellular signaling pathways. Immunosuppression mediated by non-polymorphic peptides is generally not allo-specific. On the other hand, peptides derived from polymorphic regions of HLA induce allo-specific tolerance when administered intrathymically or orally. It is proposed that these peptides block the indirect allorecognition pathway and could lead to anergy and/or deletion in the alloreactive T cell population.

Donor passenger leukocytes often migrate to and persist in recipient tissues, a phenomenon known as microchimerism [79]. In some experimental and clinical studies, the degree of microchimerism correlated with long-term allograft acceptance. This is particularly true in liver transplant recipients presumably because the liver contains a large number of passenger leukocytes including hematopoietic stem cells. The proposed mechanisms by which microchimerism leads to transplantation tolerance include the donor veto cells which kill or suppress alloreactive cells in the recipient. Others proposed that microchimerism results in persistent presence of costimulator-deficient APCs which induce anergy in recipient T cells. It is still unclear whether microchimerism is a cause of tolerance or the consequence of long-term engraftment [95].

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Donor and Recipient Transplantation Evaluation

Emilio Ramos, Matthew R. Weir, David Klassen and Susan Keay

Donor Evaluation

The waiting period for a cadaveric kidney transplant has increased considerably in the past few years, currently varying between 2 and 4 years depending on the blood type and the transplant center [42]. In comparison, living related transplants have the advantage of being performed with a minimal waiting time, usually 1 – 2 months. Living related kidney recipients also tend to have a reduced incidence of delayed graft function [90] a reduced rate of kidney rejection, and require less immunosuppression with fewer side effects. In addition, long-term graft survival is much higher for living related transplants than cadaveric transplants [78]. The half-life of a kidney allograft from an HLA identical living related donor is > 20 years, and grafts from less well matched related donors often survive for > 12 years [113]; this length of graft survival is clearly better than the average half-life of cadaveric transplants of 9 years [113]. Living related or unrelated transplants also offer the advantage of reducing the demand for a very limited supply of cadaveric kidneys [14]. Furthermore, preemptive transplantation, i.e. before the patient starts on dialysis, can be done avoiding the inconvenience and morbidity of chronic hemodialysis (HD). Although only genetically related donors were previously considered for transplantation, this is no longer necessary with the better immunosuppressive medications currently available, and indeed there has been an increase in living nonrelated transplants from spouses, friends, or distant relatives [106].

However, despite all the accrued benefit that the recipient has from live transplantation, it is of utmost importance that one considers the medical and psychological welfare of the donor, and ensures that kidney donation is done on a volunteer basis without coercion (financial or otherwise) in a well informed donor [102], with a minimal amount of medical risk. Because the recipient often gains a much better quality of life following a successful transplant, many donors feel that donating a kidney is the most positive experience of their lives and derive tremendous psychological satisfaction including increased improved self-esteem many years after donation [102].

Economic Consideration

It is important that the donor coordinates the work-up for kidney donation with the transplant center to minimize the number of days lost from work. The advent of laparoscopic donor nephrectomy performed in some centers including ours has sharply cut back the number of post-operative days, enabling the

donor to recover much faster and to return to work more quickly. Among 70 patients with laparoscopic donor nephrectomy done in our center [35], the average length of stay in the hospital was 2.2 days compared to 4.5 days for those who had an open nephrectomy. Return to normal activity was also significantly sooner for donors who underwent laparoscopic nephrectomy, with the recovery for resuming housework being 8.8 days (vs. 26.9 days for donors who underwent open nephrectomy) and return to employment being 15.9 (vs. 51.5 days). Donors who had the laparoscopic procedure also required less analgesia post-operatively and were able to resume their diet earlier than donors who underwent open nephrectomy.

Although time lost from work can be minimized and most of the cost for the donor, including the transplant evaluation, tissue typing, organ procurement and hospitalization is absorbed by Medicare [23], donors can be susceptible to financial loss. In an interesting survey of kidney donors in the U.S. regarding financial considerations, 76.7% of the 536 respondents reported no financial hardship as a result of kidney donation, 20% reported a moderate hardship, and 3.2% reported severe hardship, [103]. It is therefore, important that the donor determines whether kidney donation will affect his/her life and/or disability insurance prior to transplantation.

Initial Data Collection

Preliminary information about the donor should include a thorough medical, surgical, and psychosocial history, and a detailed physical examination [55]. Height and weight should be documented and patients who are overweight should be told about the necessity to lose weight to avoid post-operative wound complications.

Initial Studies

Initial studies include (Table 1):

- Complete blood count (CBC), blood urea nitrogen (BUN), creatinine, electrolytes, calcium, phosphorous, albumin, prothrombin time (PT), and a partial thromboplastin time (PTT);
- Serologic testing for human immunodeficiency virus (HIV-1 and HIV-2); herpes simplex virus (HSV-1 and HSV-2); Epstein-Barr virus (EBV); cytomegalovirus (CMV), hepatitis A (HAV), B (HBV), and C (HCV) viruses; Treponema pallidum (syphilis) via rapid plasma reagin (RPR) and fluorescent treponemal antibody (FTA); and Toxoplasma gondii.

Table 1. Medical Evaluation of Potential Living Donor Candidate

ABO typing
Tissue typing
Chest X-ray
ECG
Physical Examination
Complete chemistry screen
Complete blood count and coagulation studies
Urinalysis and urine culture
Spot urine for protein to creatinine ratio
Glomerular filtration rate (GFR) calculated by Cockroft-Gault method
Serology for:
HIV-1 and HIV-2, HSV-1 and HSV-2, CMV, EBV, VZV, Hepatitis A, B and C viruses, Treponema pallidum, (Syphilis), Toxoplasma gondii
PPD
Sickle cell screen
Renal sonogram (if history of polycystic kidneys)
Glucose tolerance test (if family history of diabetes mellitus)
Mammogram (patients over 50)
Pap smear
Renal arteriogram or spiral CT angiogram
Final cross-match

Table 2. Exclusion Criteria for Living Donations

– Diabetes mellitus
– Hypertension
– Proteinuria
– GFR < 80 mL/min
– Kidney stones
– Sickle trait
– Transmissible infectious disease
– Malignancy
– Psychiatric or social contraindications

– Skin test with purified protein derivative (PPD) for tuberculosis.
– Chest X-ray and electrocardiogram (ECG);
– In men: testicular examination and, in those over the age of 50, measurement of prostate-specific antigen (PSA) and a digital rectal examination;
– In women: pelvic examination and Papanicolaou (Pap) smear, breast examination, and in those over the age of 50 a mammogram (over the age of 35 if there is a history of premenopausal breast cancer in a first-degree relative);
– HLA typing;
– Urinalysis and urine culture.

Contraindications

There are relatively few contraindications to kidney donation (Table 2). These include [67]:

– Active malignancy,
– Chronic illness (specifically chronic pulmonary disease or severe cardiac disease),
– Poorly controlled psychosis,
– Active substance abuse,
– Diabetes mellitus (DM),
– Proteinuria,
– CFR < 80 mL/min,
– Hypertension and
– Kidney stones.

Relative contraindications, which require careful evaluation and possible prior treatment include:

– Active peptic ulcer disease,
– Pregnancy and
– Active Infections (including HIV).

Other Considerations

Age

In the early years of transplantation, persons were not considered for organ donation if they were over 50 years of age; however, most recently it has been shown that patients between 60 and 70 years of age can be donors if they are in good physical and mental condition [109]. In a recent survey of the United Network for Organ Sharing (UNOS), 27% of the responding transplant centers used no definite age exclusion [7]. However, it should be noted that the survival of grafts from elderly donors is not as good as the survival of grafts from younger donors probably resulting from a decrease in creatinine clearance (C_{cr}) secondary to increased presence of nephrosclerosis [74].

Renal Function

Although it is difficult to accurately measure renal function, most centers require that a donor have a C_{cr} (adjusted for body surface of 1.73 cm^2) > 80 mL/min [7]. C_{cr} needs to be carefully evaluated for each donor, including determining the adequacy of urine collection. The donor's diet should contain ≥ 1 g of protein/kg, since a low protein diet decreases C_{cr} by as much as 10 mL/min [86].

Risk of Donor Nephrectomy

– *Immediate Risk:* The normal mortality rate after donor nephrectomy is quite low (0.03%) and no different from the mortality rate of the general population, and the immediate health risks for the patient who donates a kidney are relatively small. The most important immediate risks associated with donor nephrectomy include atelectasis, pneumonia, urinary tract infection (UTI), pneumothorax, wound complication, and deep vein thrombosis with or without pulmonary embolism [14]. Peri-operative morbidity ranges between 0 and 0.23%, [7]. Elderly patients are more prone to peri-operative complications; therefore, they should have a thorough medical evaluation, including a careful evaluation of cardiopulmonary status.

– *Long-term Risk:* Unilateral renal ablation in rats results in proteinuria, hypertension, and renal failure, leading to concern that similar long-term sequelae will happen in humans following kidney donation. A review of renal function in donors 10 – 20 years after donation at 25 transplant centers found that about 30% had mild proteinuria (< 500 mg/24 hours) [32] which usually did not progress. Another review of 48 reports of patients who had donated kidneys showed a slight increase in systolic blood pressure, which could be attributed to an increase in age; again there was no evidence of progression [54]. However, relatives of patients with end-stage renal disease (ESRD) who are not donors, were also found to have a higher incidence of hypertension, probably as a result of the inherited nature of the disease [123]. Therefore, it is prudent to monitor blood pressure and proteinuria in donors, particularly if a family history of hypertension exists.

There have been anecdotal reports of patients developing ESRD after kidney donation [109]. However, the frequency of such complications is extremely small and lower than expected in the general population. Overall, the immediate and long-term risks of kidney donation are quite small and acceptable [54].

Diabetes Mellitus (DM)

Thirty percent of cases with ESRD in the U.S. are secondary to diabetic nephropathy. Therefore, one should be aware of the risk of the sibling donor developing diabetes after kidney donation. In general, siblings of patients with insulin-dependent diabetes (Type I) have an increased risk of developing DM and microvascular complications as do the offspring of parents with hypertension [29], Hispanics, Native Americans and African Americans [56]. Risk factors for noninsulin-dependent DM (Type II) include obesity, age, history of gestational diabetes, and a positive family history. Type II DM is also more common among Hispanics, Native Americans, and African Americans. Patients with gestational diabetes also have a 30 – 50% chance of developing DM within 10 years [75].

At the present time it is recommended that a fasting plasma glucose and a 75 g oral glucose tolerance test (GTT) be performed for any potential related renal donor with a family history of either Type I or Type II DM. It is also recommended that identical twins or donors below age 40 who are related to a patient with diabetic nephropathy and have a normal fasting plasma glucose and oral glucose tolerance test be screened for the presence of islet cell antibodies (ICA) and glutamic acid decarboxylase antibodies (DAG) [50]. One should be aware that certain conditions such

as malnutrition, liver disease, hypothyroidism, and corticosteroid excess, as well as the use of certain medications including oral contraceptives, diuretics, lithium carbonate, beta blockers, and analgesics can produce an abnormal GTT [56].

Polycystic Kidney Disease

Only 50% of patients with adult polycystic kidney disease (ADPKD) are diagnosed during their lifetime. It is important to identify potential donors who have silent disease.

Cyst formation is relatively rare in persons under 18 years of age, in whom it can be extremely difficult to make a diagnosis. In patients under age 30, the presence of 2 cysts (either unilateral or bilateral), detected by ultrasound establishes the diagnosis of ADPKD. In patients between 30 and 59 years of age, at least 2 cysts must be present in each kidney, and in patients over the age of 60 4 cysts must be present in each kidney to confirm the presence of ADPKD [88]. In patients over age 30, the diagnosis is usually made by ultrasonography; in persons under 30 years of age, a computed tomographic (CT) examination may be required for diagnosis. It should be noted that 3 abnormal genes have been associated with adult polycystic kidney disease; an adpkd1 gene is located on chromosome 16, an adpkd2 gene is located on chromosome 4 and a third gene (adpkd3) has no chromosome location to date [84]. In the future, persons under 30 years of age without a radiographic diagnosis may be able to be tested for these abnormal genes.

Alport's Syndrome

Most patients with Alport's syndrome have an X-linked inheritance. Therefore, asymptomatic males do not carry the abnormality, and although heterozygous females may develop hematuria, they only rarely develop renal disease. Male relatives without hematuria can be suitable donors, female relatives with hematuria or other evidence of renal abnormalities should not be considered for donation.

Isolated Microscopic Hematuria

Persons with isolated microscopic hematuria associated with proteinuria and a decrease in renal function should not be considered for kidney donation. However, many patients develop microscopic hematuria without proteinuria or renal insufficiency. In young adults the incidence of isolated microscopic hematuria can be as high as 35% [37]. These patients should be evaluated by noninvasive procedures, i.e. renal ultrasound or intravenous pyelography (IVP), to rule out the possibility of hidden malignancy. Potential donors over the age of 40 with microscopic hematuria should be evaluated more closely because of a higher incidence of malignancy in this group [71]. In addition to renal ultrasound, IVP, and a PSA test, cystoscopy should be performed. If the above examinations are negative, a kidney biopsy may be considered. A recent study of U.S. transplant centers showed that 37% of centers are willing to use allografts from donors who have microscopic hematuria if a urological evaluation and a renal biopsy are normal [55].

Hypertension

Hypertension (defined as a systolic blood pressure > 140 mmHg or a diastolic > 90 mmHg) is another contraindication for kidney donation, with most transplant centers in the U.S. rejecting all potential donors with hypertension defined by these criteria. There are,

however, patients with high normal blood pressure (> 130/85 mmHg) or "white coat hypertension" (who may have an increased blood pressure in a doctor's office, but not otherwise) who present for donor evaluation. In those patients, 24-hours ambulatory blood pressure monitoring (ABPM) has been suggested as in evaluation tool. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Report defines a normal blood pressure as < 130/85 mmHg [2].

There is no agreement in clinical practice as to whether patients with high normal blood pressure or white coat hypertension can safely serve as kidney donors, since sufficient follow-up of these patients has not been done. It is likely that some of these patients will develop hypertension (> 140/90 mmHg) over time, particulary if they have first degree relative with hypertension. But, which patients and how to properly evaluate and include or exclude them and by which criteria is not currently established (office or ABPM blood pressure).

As previously mentioned, one of the common long-term sequellae following unilateral nephrectomy is a small increment in systolic hypertension [54]. It is therefore prudent to look for other possible donors if a patient has high normal blood pressure or white coat hypertension, particularly if they have are young and have a strong family history of hypertension.

Proteinuria and Pyuria

A 24-hours urine excretion of > 150 – 200 mg of protein or > 30 mg albumin is abnormal in the absence of UTI [53]. Patients who have this degree of proteinuria should be advised not to donate their kidneys because of the likelihood of occult renal disease. Some centers, however, are willing to consider donation from persons with proteinuria if it is documented by split urinary collections to be postural in origin [7].

Pyuria (defined as > 1 – 2 white blood cells per high power field) [53] indicates the possible presence of renal parenchymal disease, usually from either chronic infection or interstitial disease. Patients with pyuria should be investigated to rule out the presence of UTI; if the pyuria persists after treatment for a documented UTI, the patient should not be considered for kidney donation.

Nephrolithiasis

Patients with renal stones are at risk for subsequent kidney disease themselves and also convey a risk to the recipient of obstruction, infection, and/or kidney parenchymal damage associated with stones [51].

Although patients who have passed one stone have a greater chance of passing a second stone [51] persons who have passed a stone only once and have been free of stone formation for > 10 years are considered to be candidates for donation.

However, a 24-hours urine determination of calcium, citrate, uric acid and oxalate should be determined for such persons to rule out metabolic causes of stone disease, and if any abnormalities are found these persons should be not be considered for kidney donation.

Recipient Evaluation

Kidney transplantation is the treatment of choice for patients with ESRD [31]. Not only is the burden of HD or peritoneal dialysis (PD) eliminated, but the patient with a successful

renal transplant has a higher quality of life [31]. Today, most patients with ESRD are potential candidates for renal transplantation and should be evaluated for this. Age or systemic conditions (such as DM) are no longer contraindications to renal transplantation, with excellent graft and patient survivals in many renal transplant centers [1]. Because of a shortage of donated organs and a growing number of patients on the transplant list, the average waiting time before transplantation is now > 2 years [42]. Therefore, it is important that potential allograft recipients be carefully selected and properly evaluated for renal transplantation. It is also important that the patient and his/her family be well informed concerning the transplantation procedure and the complications of immunosuppression, so that they can make an informed decision regarding transplantation, and be active participants in the post transplant care.

The initial clinical data that should be obtained for a potential recipient include a thorough medical, surgical, and psychosocial history and a detailed physical examination [55]. Special attention should be given to the patient's dental health and cardiovascular status as determined by the presence or absence of peripheral arterial pulses in the lower extremities. A careful abdominal examination should also be performed to look for evidence of previous abdominal operations. Initial laboratory studies should include a CBC, BUN, creatinine, sodium, potassium, cholesterol, calcium, phosphorus, albumin, PT, and PTT. Serological testing should also be performed for HIV-I and HIV-2, CMV, EBV, HSV-1 and HSV-2, VZV, HAV, HBV, HCV, *Toxoplasma gondii*, and *Treponema pallidum* (RPR and FTA tests).

Depending upon the geographic location of the transplant center, serologic tests for *Borrelia burgdorferi* (Lyme disease), *Histoplasma capsulatum*, *Coccidioides immitis* and/or *Blastomyces dermatiditis* may also be obtained as part of the baseline evaluation. If not done in the recent past, a PPD, a chest X-ray and an ECG should also be done.

In men, a testicular examination should also be performed, and a PSA level obtained and digital rectal examination done in potential recipients over 50 years of age. Potential female recipients should receive pelvic and breast examinations including a Pap smear, and women over 50 years of age should also receive a mammogram (over 35 years of age if there is a family history of breast cancer in the premenopausal years in first degree relative). HLA typing should be done and the percent reactive antibodies determined to detect previous exposure to foreign tissue antigens. In addition, certain evaluations such as an echocardiogram, thallium scintigraphy, or a voiding cystourethrogram (VCUG) may be indicated for specific patients (Table 3).

Timing of Transplantation

The transplant procedure ideally should be scheduled to coincide with the beginning of ESRD, while the patient is still in relatively good physical condition regarding nutritional status, blood pressure control, and symptoms of uremia. The time for transplantation needs to be considered for each patient individually, especially for patients with DM who develop uremic symptoms at much lower serum creatinine level than other patients. However, it is difficult to plan an exact time for transplantation since the waiting list for cadaveric kidneys varies from between 400 – 842 days depending on the center and the patient's blood type [42]. It is, of course, easier to plan the timing of transplantation when a living donor can be identified, since the transplant can take place following only 2 – 3 months of preparation.

Table 3. Pre-transplant Recipient Check-list

All Patients
Physical examination
ECG (within 6 months)
Chest X-ray (within 6 months)
Dental evaluation
Gallbladder sonogram
Pap smear
Mammogram (if over 50)
Psychosocial note from dialysis social worker
Complete chemistry screen
Complete blood count and coagulation studies
Serology for: HIV-1 and HIV-2, HSV-1 and HSV-2, CMV, EBV, VZV, Hepatitis A, B and C viruses, Treponema pallidum (syphilis) and Toxoplasma gondii
PPD
As Indicated
Dobutamine stress echo or adenosine thallium perfusion or exercise stress test
VCUG
Endoscopy
Arterial Doppler of carotids or lower extremities
Toxicology screens for substance abuse
Aortogram
Echocardiogram
Pulmonary function testing

Age

Advanced age alone is no longer considered a contraindication to transplantation. An increased number of older patients are receiving renal transplants with good patient and graft survival [49]. Vivas studied 22 patients over the age of 65 who received a cadaveric renal transplant [117]. The 3 year actuarial patient and allograft survival rate were 89% and 71%, respectively, with 12 of the 16 patients who had a functioning graft having a serum creatinine concentration < 2.0 mg/dL.

Infection

Infection is the leading cause of morbidity and mortality following renal transplantation [92]. Careful evaluation of the potential recipient is of utmost importance, making sure that he/she is free of all active infections at the time of transplantation.

Mycobacterial infections are 12 – 15 times more common in patients with uremia compared to the general population because of the immunosuppressive effect of uremia [85]. The potential recipient should be asked about a recent or a previous TB exposure. In addition, he/she should receive a chest X-ray and a PPD prior to immunosuppression. If the recipient is known to have had a positive PPD in the past, one should inquire about whether or not he/she had received prophylaxis with antimicrobial medication and the duration of that therapy. Preventive therapy with INH (given with vitamin B_6) is recommended for individuals with a positive PPD who have not received any in the past. Data is lacking for the exact duration of therapy; however, INH is usually given daily for a period of 6 – 12 months (beginning pretransplant and extending to the post transplant period if necessary). Patients with active pulmonary or extrapulmonary disease should be treated adequately with multiple drug therapy and an effort should be made to document sterilization of infected secretions or body fluids prior to transplantation.

Potential renal transplant recipients should be immunized yearly against influenza and every 10 years against diphtheria and tetanus, and should have received vaccination at some time against pneumococcus and HBV. Live attenuated vaccines should be avoided.

Infections of particular concern in the renal transplant recipient for which evaluation can be performed pre-transplantation are discussed below.

Human Immunodeficiency Virus (HIV)

Most transplant centers in the U.S. exclude patients with documented HIV infection from receiving transplantation. However, UNOS (United Network for Organ Sharing) has published a policy stating that HIV seropositive transplant candidates who are asymptomatic for HIV infection should not be denied organ transplantation, but should be advised about increased risks of morbidity and mortality because of immunosuppressive therapy [115].

Cytomegalovirus (CMV)

With the advent of antilymphocyte globulin and cyclosporine there has been an increased incidence of CMV in transplanted patients [44], making CMV the most important disease from a single pathogen among renal transplant recipients. Patients who are CMV seropositive are at risk of either reactivation of their endogenous, latent virus or infection with a second strain of CMV from a seropositive donor. Patients who are seronegative and who receive a kidney from a seropositive donor are at risk of primary infection, which is associated with an even greater morbidity and mortality than secondary or reactivated infection. CMV disease is associated with increased risk of bacterial and opportunistic infections, acute and chronic rejection, graft loss, and a higher mortality rate in renal [97] and liver [33] transplant recipients. Donor CMV seropositivity is significantly associated with kidney graft loss regardless of the recipient CMV serostatus [97]. Although the reason for the increased graft loss is not completely understood, several mechanisms have been proposed including direct cytopathic effect of the virus [97], local cytokine production, regulation of Class I and Class II major histocompatability (MHC) antigens [39, 118] and a decrease in immunosuppression given in an attempt to control the infection. Ideally, CMV seronegative patients should receive an allograft from a seronegative donor, but this is highly impractical with a limited amount of donor supply. Fortunately, the use of prophylactic therapy with antiviral drugs such as ganciclovir and/or CMV hyperimmune globulin in selected cases, has reduced disease associated with CMV infection and made it feasible to use seropositive donors for seronegative recipients [44, 104].

Epstein-Barr Virus (EBV)

Post-transplant lymphoproliferative disorder (PTLD) can result from EBV-associated proliferation of B lymphocytes in the immunosuppressed host, with a spectrum of disease ranging from a relatively benign polyclonal plasmacytic hyperplasia to a malignant immunoblastic lymphoma or multiple myeloma [59, 62, 110]. The incidence of PTLD in solid organ transplant recipients appears to depend upon both the type of organ transplanted and the immunosuppressive regimen used, with an observed incidence in the range of 1% for renal transplant recipients [72]. However, the incidence of PTLD increases significantly following the use of OKT3 and antilymphocyte globulin in renal transplant recipients [21].

Although retrospective analyses suggest that antiviral prophylaxis may be helpful in preventing this disorder [25, 57], the extent to which this disorder can be prevented in patients on increasingly powerful immunosuppressive agents is unknown.

Patients at greatest risk for the development of PTLD are the EBV-seronegative recipients of organs from EBV-seropositive donors [46]. It is therefore useful to obtain EBV immuno-

globulins IgM and IgG serologies on both donor and recipient, usually at the time of transplantation. Prior serologic assessment of the recipient is useful only if an IgG against EBV is found, since no vaccine is available at this time for the seronegative potential recipient. If a patient is seronegative prior to transplantation EBV serologies should be repeated at the time of transplantation, since EBV infection and shedding of live virus are prevalent world-wide which can result in asymptomatic seroconversion in the adult host [98].

Varicella Zoster Virus (VZV)

VZV causes chicken pox during primary infection and herpes zoster (shingles) during reactivation [120]. Both of these manifestations of disease can be particularly devastating in the immunocompromised host, including solid organ transplant recipients. Ten percent of renal transplant recipients are seronegative for VZV and at high risk for developing primary VZV infection and dissemination (including pneumonia, hepatitis, and encephalitis). Therefore, exposure to persons with active VZV infection (chicken pox or herpes zoster) should be avoided by seronegative transplant recipients. However, if exposure does occur, the consequences of such exposure can be abrogated by prompt initiation of passive immunization with Varicella-Zoster immunoglobulin (ZIG), [15], making it useful to know whether a recipient has IgM and/or IgG antibodies at the time of transplantation. Although a live attenuated virus vaccine is now available for use in VZV seronegative hosts [3], its safety and efficacy in solid organ transplant recipients remains to be determined. In contrast to the high morbidity and mortality seen in primary disease, reactivation of VZV in renal transplant patients has a more benign course, presenting usually as localized dermatomal lesions with dissemination occurring less frequently.

Herpes Simplex Virus (HSV)

HSV is another member of the herpes virus family that can cause primary, secondary, or reactivated disease in the immunocompromised patient. HSV is the earliest herpesvirus to reactivate following immunosuppression, with disease sometimes becoming manifest as early as 2 weeks post-transplant [94]. Most disease caused by HSV in the solid organ transplant recipient results from reactivation of endogenous virus, causing a spectrum of disease ranging from a localized infection of the skin or mucous membranes (e.g. a “cold sore” in the nasolabial area, or a painful anogenital lesion), to a devastating disseminated disease involving skin, the gastrointestinal (GI) tract, liver, adrenals, and central nervous system (CNS) [121]. Cases of disseminated infection following transplantation of a renal allograft from a seropositive donor into a seronegative recipient have also been reported [28]. Therefore, antiviral prophylaxis during the early post-transplant period is warranted in any case where either the recipient or donor is seropositive for HSV.

Hepatitis B

Chronic hepatitis is a major cause of morbidity in the late post transplant period [26]. Potential transplant recipients need to be screened carefully for the presence of hepatitis B surface antigen (HBsAg) prior to transplantation. Rao and Anderson reported that 38% of long term renal transplant patients

with HBV infection developed chronic progressive hepatitis, 42% of them had evidence of cirrhosis and 54% died of liver failure 10 years after transplant [87]. Huang and Lai reviewed 33 patients who were HBsAg positive; 20 of them, (60.6%) developed chronic hepatitis during a mean follow-up of 48 months. Among these 20 patients, 7 (35%) developed liver cirrhosis and 2 patients died with hepatic decompensation [47]. The major risk factor for developing chronic hepatitis in this group of patients was the presence of an elevated serum glutamate pyruvate transaminase (SGPT). Despite the high incidence of chronic hepatitis in this group (60.6%), the mortality rate was relatively low (6.1%). Huang and Lai postulated that the lower mortality rate in their series was most likely secondary to the fact that the majority of the patients were HBsAg positive prior to transplantation and none of them received antilymphocyte globulin or OKT3 [47]. These results are in marked contrast to the series reported by Parfrey [80] with a morbidity rate of 55% from liver disease in a follow-up period of 6.9 years. Harnett in his series reported a mortality rate of 34% from liver disease with a mean follow-up period of 6.8 years [41]. Chan also recently reported a more favorable prognosis in patients with HBsAg positivity; they attributed it to usage of a lower dose of steroids in conjunction with cyclosporine [16].

Nevertheless, patients who are HBsAg positive with signs of active viral replication (either HBeAg positive or those with high HBV DNA levels measured by PCR) and patients with hepatitis who are coinfected with hepatitis D virus (delta positive) are at higher risk of developing a far more advanced hepatitis following transplantation; in these patients transplantation is contraindicated and dialysis is a better option [32]. Patients who are HBsAg positive (whether or not the liver enzymes are elevated) should undergo a liver biopsy to rule out the presence of chronic active or chronic persistent hepatitis. Patients and their families should be aware of the potential risk and benefit of undergoing a kidney transplantation if the recipient is infected with HBV and they should be encouraged to participate in the final decision. Recipients who are seronegative for HBV infection (by HBsAg, HBsAb and HBeAb) should receive vaccination for HBV, prior to transplantation if possible.

Hepatitis C

Non-A Non-B hepatitis is the most common cause of chronic liver disease in the transplant population [92]. Most cases of non A non B hepatitis are caused by HCV.

Using recent assays to detect HCV [105], it has become apparent that the previously expected incidence of HCV among renal transplant donors and recipients was underestimated. The incidence of hepatitis C seropositivity among the dialysis population can be as high as 60%. However, it is difficult to predict which patient will progress and how fast, with severe liver disease occurring as early as 2 years or as late as 20 years after transplantation [20]. HCV is present in body fluids at much lower concentrations than HBV and therefore it has a lower degree of infectivity, with transmission usually occurring as a result of transfusion of blood or blood products from infected HCV donors. Although antibodies to HCV do develop, they do not eradicate the virus and confirm no immunity, with 85% of these patients becoming chronically infected.

Although patients who are hepatitis C antibody positive are at an increased risk of developing chronic active hepatitis, it is difficult to assess the final impact of hepatitis C on morbidity and mortality in transplant recipients

Table 4. Primary Renal Disease Recurrence after Transplantation

	Recurrence Rate	Graft Loss in Patients with Recurrence	Comments
Focal segmental glomerulosclerosis	20 – 30%	30 – 40%	Younger patients with previously aggressive disease are at higher risk
Anti-GBM disease	5 – 50%	unusual	Delay transplant for 6 months after documentation of negative antibody
Membranous nephropathy	3 – 25%	minimal	HLA-identical transplants may have increased risk
IgA nephropathy	40 – 60%	< 20%	More common in living related transplants
Type I membranoproliferative glomerulonephritis	20 – 30%	20 – 30%	Difficult to distinguish from transplant glomerulopathy
Type II membranoproliferative glomerulonephritis	50 – 100%	10 – 20%	May have long course to graft failure

since the follow-up period in published studies has not been long enough. Several genotypes of HCV have also been identified, allowing a secondary infection from an HCV seropositive donor into an HCV seropositive recipient [101]. Patients with hepatitis C develop slow, progressive liver disease, usually beginning several years after transplantation [48]. However, the coexistence of hepatitis B and C leads to a more aggressive form of liver disease with a higher incidence of hepatocellular carcinoma [20]. It is therefore prudent to implement the same policy that is used with HBV seropositive patients including performance of liver biopsy (in seropositive potential recipients with either normal or elevated liver enzymes) to better assess the extent of liver pathology prior to transplantation.

Recurrent Primary Disease in the Renal Allograft

Many primary renal diseases can recur in the transplanted kidney (Tables 4 and 5) [88]. In addition, de novo disease other than chronic rejection can also be seen in the transplanted kidney. Transplant glomerulopathy, a form of chronic rejection that resembles Type I membranoproliferative glomerulonephritis (MPGN) [79], is one of the most common forms of glomerular diseases seen in kidney allografts.

This pathological entity is most likely secondary to vascular endothelial cell injury, with microthrombosis leading to endothelial and mesangial cell proliferation and reduplication of the basement membrane [40]. MPGN is usually seen in patients with a previous episode of acute rejection and invariably leads to ESRD and loss of the allograft.

Table 5. Secondary Renal Disease Recurrence after Transplantation

	Recurrence Rate	Graft Loss in Patients with Recurrence	Comments
Henoch-Schönlein purpura	10 – 15%	10 – 20%	delay transplantation for 6 – 12 months after loss of purpura
Lupus nephritis	rare	0%	
Hemolytic uremic syndrome	15 – 25%	10 – 20%	Avoid Living Related Donor in familial HUS
Diabetic nephropathy	100%	5%	Graft loss is late
Amyloidosis	2 – 30%	30%	

The risk for recurrent disease varies greatly among the different kinds of glomerulopathies. Although recurrent kidney disease of all types is seen in < 20% of patients, 2 – 5% of recipients lose their grafts from recurrent disease. However, these estimates are difficult to interpret since many patients with ESRD do not have a biopsy-proven diagnosis prior to dialysis, and post-transplant biopsies are usually performed only in patients with clinical disease.

Focal Segmental Glomerulosclerosis (FSGS)

The recurrence rate for idiopathic (or primary) FSGS in the renal allograft is 20 – 30% [108], but can be as high as 50% in patients younger than 15 years of age. If the clinical course of the initial disease progresses rapidly with the development of ESRD within 3 years of diagnosis, the recurrence rate in the allograft is > 80% [112], whereas patients whose clinical course progresses more slowly (> 3 years from proteinuria to ESRD) have a recurrence rate between 10 – 20% [60]. In addition, if recurrent disease occurs in the first allograft, there is a higher incidence of recurrence in subsequent allografts [112]. Mesangial proliferation in association with typical FSGS lesion in the native kidney is also a risk factor for recurrence [88], and patients who receive an HLA-identical kidney have a higher incidence of recurrent disease.

In patients who developed nephrotic range proteinuria in the immediate post transplant period, the rate of graft loss is 30 – 40% in comparison to patients who develop proteinuria ≥ 3 months after transplantation with de novo FSGS have a better allograft survival [88]. Some patients with FSGS have been shown to have an albuminuric factor which increases proteinuria [95]. In these patients the use of plasma exchange or protein A immunoabsorption seems to reduce proteinuria transiently [24]; however, more prospective studies are needed to further characterize the albuminuric factor and the effect of plasma exchange or protein immunoabsorption. Allografts from living related donors should be

used with caution in patients who are at high risk for recurrent disease.

Although recurrent disease in first allograft is common and in the second allograft can be as high as 85%, recurrence should not be a contraindication for retransplantation since a second cadaveric transplant has been performed successfully in many cases [107]. However, it is important to emphasize that the secondary forms of FSGN do not recur.

Membranous Glomerulonephritis (MGN)

Most cases of MGN seen in transplant patients are de novo disease occurring in 75% of the cases [6] and resulting in a graft loss rate of 12 – 50%, [66]. Although the incidence of recurrence is usually only 3 – 7%, incidences up to 25% have been reported to occur [66].

However, it can be difficult to interpret these data since other factors including renal vein thrombosis, medications or chronic rejection can also result in membranous changes in the kidney allograft.

Patients who receive an HLA-identical kidney have a higher incidence of recurrence of MGN and develop proteinuria at an earlier stage post transplantation than patients who receive a cadaveric kidney (in whom proteinuria usually appears 7 – 25 months after transplantation) [55]. As with FSGF, caution is urged in using living related donors for these patients.

IgA Nephropathy (IgAN)

IgAN is the most common cause of glomerular disease worldwide; however, < 20% of these patients develop ESRD. The recurrence of IgA nephropathy in the allograft is about 50%. Patients typically present with hematuria and proteinuria, and graft loss is relatively small (< 10%) [77]. Although the patient who receives a living related kidney has a higher incidence of recurrence, the low rate of graft loss does not preclude living related transplantation [55].

Odum et al. [77] have suggested that the incidence of recurrent disease and/or graft loss is higher with increasing length of time post transplantation, suggesting that it may be premature to assess the frequency of recurrence and graft loss in these patients. In most studies the use of cyclosporine did not prevent the recurrence of immune deposits in the transplanted kidney.

Type I Membranoproliferative Glomerulonephritis (MPGN)

The incidence of recurrence of Type I MPGN in the allograft is about 20 – 30% as is the incidence of graft loss [13]. Although some studies have shown an incidence of recurrence up to 70%, these studies are difficult to interpret as discussed above, since many cases of post transplant glomerulopathy (which resembles type I MPGN) were included. Cyclosporine also does not prevent recurrent MPGN in the allograft. Because of the high incidence of graft loss associated with this disease, and a greater chance of recurrence associated with living related donors, it may be prudent to avoid living related transplantation in these patients.

Type II Membranoproliferative Glomerulonephritis (MPGN)

Although the recurrence rate for type II MPGN is as high as 55 – 100% in the allograft [78], the rate of graft loss is only 10 – 20% [30]. Histologically discreet subendothelial

dense deposits on electronmicroscopy are indicative of recurrence; however, measurements of C3 or C4 are not helpful in predicting recurrent disease. Male patients who present with extensive proteinuria or rapidly progressive disease have a much higher incidence of graft loss [30]. In patients with aggressive recurrent disease, plasma exchange has been advocated [75]; however, no treatment is effective for most patients at the present time. Subsequent recurrent disease in a second graft has also been reported.

Anti-glomerular Basement Membrane (GBM) Disease

The histological recurrence rate of anti-GBM disease in the allograft is quite high (up to 50% of cases) with 25% of these patients developing clinical manifestations [66]. It is, therefore, very important to monitor anti-GBM antibodies and postpone transplantation until they are undetectable over a period of 6 – 12 months [66]. Graft loss secondary to anti-GBM disease seems to be rare. The specific recurrence rates for patients with idiopathic rapidly progressive glomerulonephritis (RPGN) or crescentic glomerulonephritis (CGN) secondary to infection, IgAN, systemic lupus erythematosus (SLE), or mixed cryoglobulinemia are unknown.

It should be noted that patients with Alport's disease can also develop anti-GBM disease following transplantation [69].

Henoch-Schönlein Purpura (HSP)

Evidence for recurrence of this disease, i.e. mesangial hypercellularity and IgA deposits in the allograft, can be found in approximately 30% of adults and up to 75% of children; however, symptomatic disease recurs in < 10% of cases [43].

Transplantation should be delayed in patients with active disease, since the associated graft loss rate is quite high [43]. Current recommendations include a waiting period of 1 – 2 years after the clinical manifestations have become quiescent.

Systemic Lupus Erythematosus (SLE)

The recurrence rate of SLE in the transplanted allograft is very rare, occurring in < 1% of cases [38]. In the rare individual who develops systemic manifestations of recurrent SLE consisting of Raynaud's phenomenon, malar rash, arthralgias, and/or proteinuria, the most common histologic finding has been the presence of mesangial proliferative glomerulonephritis. Several treatments have been advocated including pulse steroids, or a combination of plasmapheresis, chlorambucil and monthly intravenous (IV) cyclophosphamide therapy [38]. Although there have been reports of successful transplants in patients with clinically active disease (with a positive serology including high levels of antinuclear and anti-DNA antibodies and low complement levels), it is probably wise to postpone transplantation until the disease has become more quiescent both clinically and serologically [38].

In addition, patients with the lupus anticoagulant are prone to thromboembolic episodes and should be anticoagulated post-transplant.

Hemolytic Uremic Syndrome (HUS)

The diverse etiologies of hemolytic uremic syndrome include pregnancy, infections, malignant hypertension, systemic sclerosis, severe acute vascular allograft rejection, oral contraceptives and use of chemotherapeutic

agents, including cyclosporine, OKT3, or antilymphocyte globulin. Patients with this disease can develop thrombocytopenia, microangiopathic hemolytic anemia and acute renal failure (ARF). The recurrence rate in the adult usually varies from 15 – 25% of cases, whereas in the pediatric population the recurrence rate is only about 10%. However, recurrence of disease is associated with loss of 50% of allografts [116]. Risk factors for recurrence includes early transplantation, thus it is recommended that patients wait 3 months after the acute disease has subsided before undergoing transplantation.

Remuzzi et al. [91] have shown that patients with HUS and family members of patients with HUS have a decreased level of a plasma factor which stimulates endothelial prostaglandin synthesis associated with thrombosis. Living related donors should be used with caution for patients with HUS since the recurrence rate is much higher in recipients of allografts from these donors. Various therapies with varying degrees of success, including plasmapheresis, have been tried in patients with recurrent disease [60]. Although tacrolimus (FK506) and cyclosporine have been shown to induce de novo HUS, their use has not been associated with recurrence of disease and therefore is not contraindicated.

Diabetes Mellitus (DM)

DM is the most common cause of ESRD in this country, accounting for about 35% of patients with ESRD. Virtually 100% of diabetic patients who are transplanted develop histological changes in the allograft including glomerular basement membrane (GBM) thickening at 2 years and hyalinization of both the afferent and efferent arterioles at 4 years [10]. The classical Kimmelstiel-Wilson lesions, however, are rarely seen [65]. Although many patients eventually develop proteinuria and a slow decline of renal function, graft loss secondary to recurrence of diabetic nephropathy is rare.

Simultaneous kidney/pancreas transplant seems to protect the kidney from developing diabetic nephropathy, possibly because good blood sugar control can prevent or delays the onset of diabetic nephropathy [10].

Amyloidosis

Transplantation may be considered for patients with amyloidosis secondary to chronic inflammation especially if the extrarenal manifestations in organs such as the liver, heart, and spleen are absent.

However, the mortality rate following transplantation for secondary amyloidosis is quite high, approaching 50% at one year post transplant in patients with more severe extrarenal manifestations [81]. Mortality in these patients is mainly secondary to infections, cardiac decompensation and cerebral vascular accidents. Amyloidosis recurs in 20 – 30% of allografts with graft loss approaching 30% [66].

Primary Oxaluria

Primary oxaluria is an inborn error of glyoxylate metabolism secondary to a deficiency of glyoxylate immunotransferase, an enzyme which is found primarily in the liver. Patients develop renal failure secondary to the rapid accumulation of oxalate and calcium oxalate stones in the kidneys [96]. The recurrence rate for disease in the allograft is quite high unless transplantation is done early in the disease when the creatinine clearance is ≥ 20 – 25 mL/min [118]. Aggressive dialysis to deplete the oxalate stores has been recom-

mended, along with the use pyridoxine which acts as a coenzyme in the conversion of glyoxylate to glycine [67]. However, the rate of graft loss even with the above manipulations is still high. It may be reasonable to consider a combined liver/kidney transplant for these patients since the new liver can provide the missing enzyme [96].

Sickle Cell Disease

There is a limited amount of information regarding graft loss in sickle cell disease, but it is known that the improved hematocrit following transplantation is associated with more severe sickling crisis, which can lead to graft loss.

The one year graft survival reportedly varies between 25% and 67% in patients with this disease [18]. It is, therefore, prudent not to transplant patients with frequent sickle cell crisis.

Cancer

Immunosuppression favors the growth of cancer cells and every effort should be made to insure that pre-existing malignancies in the recipient are totally eradicated prior to transplantation [82]. Unfortunately, although the patient may have no gross evidence of remaining tumor, occasionally residual cancer cells remain in situ, or in distant micrometastases. According to the Cincinnati Transplant Tumor Registry (CTTR), a waiting period of 5 years following the apparent cure of a pre-existing carcinoma eliminates 90% of recurrences [82]; however, it may not be practical for elderly individuals or very young patients to wait this long. A waiting period of 2 years eliminates about 53% of overall recurrences [55], 91% of patients with Wilm's tumors, 61% of patients with squamous cell skin cancer (other than melanoma), and 61% of patients with symptomatic renal tumors [82], but only 13% of recurrences of colorectal cancer, 19% of recurrences of breast cancer, 40% of recurrences of prostatic cancer, and 50% of patients with recurrent malignant melanomas. Therefore, for patients with these latter malignancies, a waiting period between 2 – 5 years after apparent cure is recommended [82]. A similar waiting period of 2 – 5 years following apparent cure is recommended for lymphoma, invasive uterine and invasive cervical cancers.

However, since more favorable prognosis is associated with lobular in situ carcinoma of the breast, Duke's A carcinoma of the colon, focal carcinomas of the prostate, focal in situ

Table 6. Recommended Tumor-free Waiting Periods prior to Transplantation

Malignancy	Waiting Period
Basal cell skin In situ bladder In situ cervical Incidental renal cell Clarke's level I melanoma Duke's A colon In situ lobular breast In situ prostate	None
Uterine Lymphoma Squamous cell skin Wilm's tumors	2 years
Breast Melanoma Invasive cervical Colorectal Renal Prostate Testicular	2 – 5 years

carcinoma of bladder, basal cell skin cancer, in situ carcinomas of uterus, and Clark level I melanomas, patients with these specific tumors may be considered for transplantation earlier.

Renal and Bladder Tumors

Among 71 patients in the CTTR who were incidentally discovered to have renal cell carcinomas at the time of transplantation, none had a recurrence in the allografts [83]. However, if a renal tumor is large or has invaded outside the renal capsule, a waiting period of 3 years following apparent cure is advised before transplantation.

In comparison, recurrence of Wilm's tumor occurred in 91% of patients transplanted within 2 years of apparent cure [83], with a mortality rate of about 50% if the transplant is done within a year after apparent cure and about 27% when transplantation took place > 1 year after apparent cure [82]. It is therefore important that patients with Wilm's tumor wait for at least 2 years before transplantation. In patients with invasive bladder cancer a 2 year waiting period also eliminates about 70% of recurrences [82].

Testicular Cancer

Testicular examinations should be performed routinely in patients awaiting kidney transplantation, including regular self examination. The recurrence rate of testicular carcinoma following transplantation has been low (around 3%) perhaps because many patients have had a long (2 – 5 year) waiting period before transplantation with patients having invasive tumor waiting up to 5 years before transplantation [55]. Because undescended and atrophic testes are more prone to develop seminomas than normal testes, [82], it is recommended that they be removed prior to transplantation.

Breast Cancer

The recurrent rate for breast cancer in the CTTR data is 25%. Ten of the sixteen patients to develop recurrence were treated for < 5 years before transplantation.

It may therefore be prudent to have a waiting period of at least 2 years or up to 5 years if there is axillary involvement, bilateral disease or inflammatory histopathology [55]. Women should also be encouraged to do self breast examinations, and a mammography should be routinely be performed yearly after age 50 (after age 35 if there is a history of breast cancer in the premenopausal years in any first degree relative). As mentioned above, patients with in situ lobular carcinoma have a much better prognosis, and a shorter waiting period may therefore be indicated for these patients.

Other Risks

Urologic Disease

A renal imaging study (typically an ultrasound) should be performed on all candidates to ensure that there is no potentially reversible cause of renal disease, as well as to look for evidence of acquired cystic disease in patients who have been on dialysis for a prolonged period of time. A history of bladder dysfunction should also be sought for all potential transplant candidates. While it is probably not necessary to perform a VCUG in all patients, an extensive urologic work-up including retrograde cystoscopy is recommended for chil-

dren and adults with a history of bladder or genitourinary abnormalities [100].

Pretransplant native kidney nephrectomy is only required for certain indications including infected stones, reflux, renal carcinoma [55], and polycystic kidneys (if they are massive or develop recurrent episodes of infections or bleeding). For patients seeking a second transplant, removal of the first failed transplant is only required if the allograft is an ongoing source of morbidity (e.g., infection, bleeding, pain, or fever).

Patients with existing ureteral diversion procedures should be evaluated to ascertain whether the native bladder can be used, and patients with bladder dysfunction should be warned of the potential necessity for intermittent self catheterization following transplantation. If the bladder cannot be used, use of the prior diversion is possible although there is an increased risk of infections and other urologic complications.

Gastrointestinal (GI) Disease

While it is probably not necessary to routinely screen asymptomatic transplant candidates for upper and lower GI disease, symptomatic patients should be evaluated thoroughly. If a peptic ulcer has been recently diagnosed, healing should be confirmed prior to transplantation. Many transplant programs prescribe H_2-receptor blockers prophylactically posttransplant [5]. Diabetic patients need to be screened for asymptomatic cholelithiasis since post-transplant cholecystitis may be difficult to recognize. Non-diabetic patients with symptomatic cholelithiasis and diabetic patients with asymptomatic cholelithiasis should undergo pretransplant cholecystectomy [63].

Pretransplant pancreatitis is also a source of concern since post-transplant pancreatitis has a high morbidity [12] and prednisone, azothiaprine, cyclosporine, CMV disease, hypercalcemia, and hyperlipidemia can all cause pancreatitis following transplantation. Therefore, if a correctable cause can be recognized, it should be addressed prior to transplantation.

Systemic Disorders and Medications

Obesity is a well-defined risk factor for post-transplant morbidity, and although it is rarely an absolute contraindication to transplantation, obese patients should be forewarned [9]. Every attempt should be made to encourage weight reduction pretransplant, although this may be difficult in dialysis patients, since their ability to exercise is limited.

Patients with type I DM are faced with several transplantation options and it is critical that they are fully appraised as to the potential risks and benefits of each. The results of cadaveric and living donor transplantation in diabetic patients are not different from those in non-diabetic patients as long as covert vascular disease is considered in the work-up. Simultaneous kidney/pancreas transplantation with bladder or enteric drainage may also be reasonable. The unequivocal benefit of this procedure is its capacity to make the patients “non-diabetic” and thereby improve their quality of life. Unequivocal proof that the combined procedure reduces the long-term complications of diabetes is not yet available, although there are data that suggest improvement of diabetic autonomic neuropathy [58] and subclinical nephropathy documented histologically [8]. However, the combined procedure in patients over 45 years of age is associated with increased surgical morbidity, a higher incidence of reoperations, prolonged hospital admission and an increased incidence of episodes of acute rejection [19, 114]. Therefore, many programs do

not offer the combined procedure to older diabetics or to those with evidence of significant coronary or peripheral vascular disease.

Patients with evidence of symptomatic secondary hyperparathyroidism on dialysis, refractory to medical management, should be considered for pretransplant parathyroidectomy [55], to minimize the incidence and severity of post-transplant hypercalcemia [45]. A subtotal parathyroidectomy is preferred to prevent post-transplant hypocalcemia.

The medication regimen of all transplant candidates should be reviewed to identify drugs that may interact with cyclosporine or FK506 [99], with particular attention paid to anticonvulsants. Every attempt should be made to discontinue barbiturates which may make it difficult to achieve therapeutic levels of immunosuppression. Dilantin can be used postoperatively as long as the dose of cyclosporine is modified. If seizures are infrequent, a neurologic evaluation should be sought for the possibility of discontinuing anticonvulsant treatment.

Psychosocial Issues

Renal transplantation requires frequent post-transplant visits, numerous urine and blood lab tests, and in many cases a substantial amount of medications to be taken on a daily basis and on a regular schedule. In addition, there is the inconvenience and expense involved in traveling to the transplant clinic, time off from work and/or from the domestic responsibilities that the patient may have. Patient noncompliance could be an episodic phenomenon or it could be more persistent leading usually to complications and graft loss [36]. It is therefore, the responsibility of the transplant team to assess the psychosocial issues of the transplant recipient. A thorough pyschosocial history about any cognitive or emotional problems in the recipients and or in their families should be obtained, since some psychiatric disorders are hereditary. In patients who have been on chronic dialysis, noncompliance with the dialysis schedule, poor adherence to the renal diet and fluid restriction, or noncompliance with medications predict poor outcome post-transplant (including missed transplant visits and rigorous adherence to medications). Other factors associated with noncompliance include young age (preadolescents and adolescents), living alone, living more than 100 – 150 miles from the transplant center, and stable post-transplantation clinical status for a period of 4 – 5 years [27]. Patients with psychosocial issues should be referred to a psychiatrist for evaluation and treatment before transplant to have a baseline of their psychological background [61]. The psychiatrist can also help to coordinate the best timing for transplantation. Spouses or family members should be questioned about mild degrees of impaired memory, inability for sustaining attention or mood alterations; in cases of impaired cognitive functions, severe anxiety disorders, history of depression, psychosis or psychiatric disorder, the patient should be referred to a psychiatrist for evaluation and treatment prior to considering transplantation. It is also desirable to have a baseline psychological profile prior to transplantation in case problems arise following transplantation.

Alcohol and Substance Abuse

Alcohol and substance abuse is a major problem in the renal transplant recipient, since it can interfere with the ability of the patient to adhere to the frequent clinic visits and their rigorous medication schedule [27]. Therefore, patients with substance or alcohol abuse

should be counseled and if possible referred to a rehabilitation center. Follow-up for compliance should be rigorously monitored; many transplant centers require a period of 6 months to one year of abstinence before activating the patient on the transplant list.

Cardiovascular Disease

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality after renal transplantation [52], and patients should therefore be carefully screened for the presence of CAD prior to renal transplantation. Diabetic patients with renal failure have an 8 – 15 times higher chance of dying from CAD compared to diabetic patients without renal failure [122], and 25 – 40% of asymptomatic diabetic patients with ESRD have significant disease in one or more coronary arteries by angiography [64].

Patients who are not sedentary with no history of atherosclerotic vascular disease, DM, hypertension or smoking, and who have an HDL > 35 mg/dL and an LDL < 100 mg/dL, can be safely screened by obtaining a medical history, a physical examination and an ECG. Patients who have a history of CAD should be evaluated with coronary angiography; if critical coronary artery stenosis is present they should be considered for angioplasty or revascularization prior to renal transplantation. Symptomatic patients with CAD should also be considered for revascularization, angioplasty, or stent placement prior to renal transplantation each of which has been shown to decrease morbidity and mortality in these patients.

Patients with diffuse CAD who are not revascularization candidates and patients who have a poor ejection fraction generally should not be considered for transplantation [64]. In addition to consideration of coronary revascularization, aggressive risk factor intervention for CAD should be addressed.

In the asymptomatic diabetic patient over the age of 45 with over 25 years duration of DM, the high likelihood of the presence of CAD warrants a coronary angiogram to rule out the presence of significant CAD; however, in patients under the age of 45 with a history of DM of < 25 years duration or with a negative history of smoking and without any evidence of ischemic disease by electrocardiogram, a less aggressive approach can be considered including an exercise thallium scintigraphy or dobutamine stress echocardiography [63]. Dobutamine stress echocardiography and other forms of pharmacologic stress testing are particularly useful for evaluating diabetic patients who cannot exercise to reach a target heart rate because of peripheral vascular disease or severe diabetic neuropathy. If any of the above tests is positive, one should proceed to angiography; if a significant stenosis is identified, angioplasty or coronary artery bypass grafting should be considered.

Patients with a history of transient ischemic attacks (TIA) or a recent (within 6 months) cerebral vascular accident (CVA) need to be referred to a neurologist for evaluation.

Most transplant centers perform routine carotid Doppler studies in patients with vascular disease or risk factors for coronary artery disease. Although the Asymptomatic Carotid Atherosclerosis Study (ACAS) [70], indicated that endarterectomy is generally beneficial in patients with > 60% stenosis, there are no specific prospective studies in transplant recipients, and therefore the treatment of carotid disease should be individualized.

Patients with ADPKD have a higher incidence of intra-cranial aneurysms [17]. However, noninvasive studies such as a magnetic resonance imaging (MRI) or a high-resolution tomography are usually limited to those pa-

tients who have a family history of intracranial bleed or death from a CVA of unknown etiology. In patients with severe peripheral vascular disease (PVD) including the absence of femoral pulses, an arteriogram should be performed to rule out the presence of aortoiliac disease which may necessitate reconstructive surgery prior to renal transplantation.

Lung Disease

Renal transplantation is usually done extraperitoneally in the lower abdominal quadrant, resulting in few lung complications. Patients with no history of smoking and no lung disease need not be evaluated preoperatively for lung disease. Patients with a history of cigarette smoking should be strongly advised to stop smoking. Pulmonary tests should be performed if there is any clinical evidence of emphysema or chronic obstructive pulmonary disease (COPD), and adequate pre- and postoperative respiratory therapy in patients with these diseases has been shown to be beneficial. Transplantation is contraindicated in patients with active pulmonary infection (including bacterial, fungal or viral infection). Patients with asthma that is well controlled with medications should not have an increase in pulmonary complications during or after transplantation.

Transplant recipients with a history of pulmonary disease who undergo a thoracic or upper abdominal surgical procedure however, are more prone to pulmonary complications. These patients therefore should have a more thorough evaluation and perioperative respiratory treatment, since the incidence of pulmonary complications in these patients is high [124].

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Renal Transplant Surgery, Perioperative Care and Postoperative Complications

Thomas A. Abbruzzese and Nicholas L. Tilney

Introduction

Commensurate with its establishment as an effective treatment for many individuals with end-stage renal disease (ESRD), kidney transplantation has undergone striking advancements in both allograft function and patient survival. In addition to more effective immunosuppression, there has been consistent progress in the understanding and care of patients with renal failure, in the refinements of operative techniques and in the identification and management of postoperative complications. Indeed, results were improving progressively before the advent of cyclosporine (CyA) in the early 1980's as clinical experience with these challenging patients accrued.

The potential for mechanical difficulties stems from the very nature of the renal transplant procedure. Placement of the graft involves isolation and anastomoses of major arteries and veins in a lymphatic-rich area, as well as implantation of the ureter into the recipient bladder, ureter, or, occasionally, into an ileal loop. The major postoperative complications are shown in Table 1. The importance of prompt recognition and aggressive and opportune repair of any such complications ensures that few losses occur secondary to surgically related problems.

Table 1. Postoperative complications of renal transplantation.

- Perinephric infection
- Acute hemorrhage
- Vascular complications
- Urine leak
- Ureteral obstruction
- Lymphocele

Preoperative Strategies

The potential recipient must be evaluated (see Chapter III-2) and then re-examined when a kidney becomes available, as the waiting time for the organ may have been lengthy and pre-existing medical conditions may have changed or progressed. Obvious abnormalities such as severe anemia, fluid, electrolyte and metabolic defects must be corrected. Accurate assessment of volume status is critical, particularly if the patient has been dialyzed immediately preoperatively. Hypovolemia increases the possibility of delayed graft function; generous replacement with crystalloid and oncotics is necessary during and immediately after the operation. Conversely, hypervolemia should be corrected. Indeed, those patients on chronic dialysis will almost invariably benefit from a treatment

Table 2. Management of cadaver donors.

Initial goals:
- Correct acid-base imbalances
- Optimize lung function
- Restore intravascular volume
- Normalize blood pressure
- Maintain hematocrit > 30%
- Treat severe hyperglycemia, central diabetes insipidus
- Treat disseminated intravascular coagulopathy

Specific considerations:
- Dopamine is the pressor of choice for treatment of hypotension
- Maintain brisk diuresis (urine output > 200 ml/hour)

within the 24 hours preceding the transplant to maintain electrolyte and volume homeostasis. Some clinicians have advocated monitoring central venous pressure (CVP) or placing a pulmonary arterial catheter for accurate assessment of volume and cardiac performance in older patients, particularly those with impaired cardiac function. Albumin is particularly effective for volume expansion in chronic renal failure (CRF) patients, as it can mobilize excessive interstitial fluid into the vascular space. A relatively large dose (1.2 – 1.6 g/kg) administered intraoperatively has been shown to improve early graft function, increase organ survival, and lower mortality [1].

For potential cadaver donors, general management guidelines begin with an assessment of the admission history and physical exam, hospital course, temperature, fluid balance, hemodynamics, medications, infections and organ function (Table 2).

Anesthesia in the Transplant Recipient

The choice of anesthetic technique may depend upon the adequacy and timing of the preoperative dialysis, the pharmacological characteristics of different agents and alterations in hemodynamic or volume status. Anemia, if chronic, is not a contraindication to prompt anesthesia for transplantation, as patients with CRF function well with relatively low levels of hemoglobin. If the hematocrit (HCT) is stable, there is no need to correct it acutely to ideal levels before surgery; transfusions can be administered during the operation if necessary. The increased use of erythropoietin (EPO) has dramatically reduced the transfusion needs of the dialysis population.

Important practical considerations in the overall anesthetic care of the transplant patient should include the appreciation that peripheral veins for cannulation are usually limited in number and quality; this can create a large problem for inexperienced anesthesiologists. Functioning dialysis accesses should never be used as an intravenous (IV) route except in emergencies, as they are prone to thrombosis. Blood pressure may also be difficult to measure in these individuals because of multiple previous surgical procedures on available arm vessels. The sphygmomanometer cuff should never be placed proximal to a fistula and inflated even intermittently during the operation, as occlusion of the vascular access will almost inevitably follow. There is little so disheartening for patient and surgeon alike to be faced, early in the postoperative period, with both a non-functioning kidney and a clotted access.

Systolic blood pressure should be maintained > 120 mmHg intraoperatively to

achieve adequate perfusion of the newly revascularized organ and to overcome arterial vasospasm. Some anesthetic agents can induce relative hypotension by decreasing sympathetic tone, with resultant vasodilatation and venous pooling. Plasma volume may still be reduced and transcapillary filling ongoing in patients who were hemodialyzed just prior to transplantation. Baroreceptor compensation, already abnormal in the uremic "milieu," may be further impaired by the effects of anesthetic drugs. All these factors together emphasize the need for optimal hydration with perioperative monitoring [2].

Changes in the pharmacokinetics of anesthetic agents should be considered, as those with renal failure are unable to eliminate many drugs, their metabolites or their conjugates. The pharmacokinetics of some neuromuscular blocking agents may be altered by severe acidosis or electrolyte imbalances, or they themselves may produce acute hyperkalemia, as exemplified by the effects of succinylcholine. Galamine is contraindicated because it is excreted primarily by the kidney and it is not dialyzable. The kinetics of narcotic agents like morphine or fentanyl may vary amongst individual patients, with some exhibiting markedly decreased clearance – possibly related to high blood urea nitrogen (BUN) levels – leading to prolonged postoperative ventilatory depression [3]. Atracurium is widely used as an anesthetic agent for renal failure patients because its metabolism occurs at physiological pH and temperature and not by breakdown in a particular organ. Elimination of vecuronium and rocuronium may be prolonged because the volume of distribution of these drugs in renal transplant patients is greater than that of normal controls [4]. Potent vapor anesthetics, such as halothane, enflurane and isoflurane may be administered with relative safety. Spinal or epidural regional anesthesia is often used successfully for kidney transplantation, although prolonged bleeding time and partial thromboplastin time remain a contraindication to those techniques.

Calcium channel blockers have been advocated by some to prevent or at least reduce the severity of post-ischemic renal failure when given prior to or after the ischemic insult. Beneficial effects may occur when they are given before the vascular anastomosis [5, 6, 7]. This is probably due to the ability of these agents to ameliorate renal vasoconstriction: they counteract both the direct vasoconstrictive properties of CyA as well as its indirect effects associated with up-regulation of endothelin and thromboxane [8]. This group of drugs can also potentiate the immunosuppressive capacity of CyA [9], and may block intracellular calcium overload induced by ischemia or toxic stimuli [10]. Recent data also suggest that they improve graft function and survival over the long term by mitigating CyA-associated renal injury [11, 12].

Mannitol is administered in many centers during revascularization of the donor kidney as it may reduce the incidence of acute tubular necrosis [13]. This prophylactic effect is not shared by other diuretics, although the agent is not an effective treatment for early or established non-function [14].

Delayed Graft Function

Overall ischemia suffered by an organ graft is the sum of any warm ischemic interval before and during removal from the donor, the period of cold ischemia associated with organ preservation and storage, and the time of revascularization to the recipient circulation. The physiologic and metabolic changes in anoxic tissues have been well described [15].

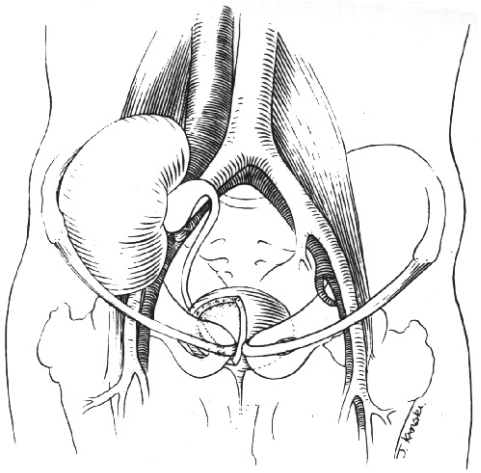

Figure 1. When the kidney graft is transplanted to the ipsilateral side of the recipient, the ureter and the collecting system may still be kept medial by placing the organ uside down. The ureter is reversed toward the bladder in a gentle curve. (with permission of WB Saunders, Philadelphia)

The principal clinical manifestation of ischemia/reperfusion injury is delayed graft function, an important entity that may pose diagnostic dilemmas and may affect ultimate graft behavior (see Chapter III-5). Histologically, the hallmark of ischemia/reperfusion injury is acute tubular necrosis (ATN). Several clinical series also show that ischemia reperfusion predisposes to acute renal failure (ARF) while the incidence of acute rejection is increased significantly in kidneys with initial graft dysfunction. When both insults occur, graft success is significantly decreased as compared to that noted with only one or no initial injury [16]. There are presently no uniformly effective ways to prevent ischemia/reperfusion injury and minimize the development of subsequent delayed graft function, although some claim that the use of mannitol, volume expansion and calcium antagonists may improve microcirculation and relieve vasospasm in this setting [17].

Surgical Technique of Renal Transplantation

The iliac approach for the placement of kidneys in adults is used by all in the field. The anesthetized patient (general or regional) is placed supine upon the operating table. The bladder is catheterized with a Foley catheter and irrigated with a bactericidal solution, about 75 ml of which is retained intravesically by clamping the drainage tubing. The lower abdomen, genitals and upper thighs are scrubbed and the patient draped appropriately. A curvilinear incision is made between pubis and iliac crest. As the incidence of diverticulitis is relatively high in the dialysis population, the right side of the patient is usually chosen, although either side can be used depending on the donor kidney. It is usual to place the kidney in the contralateral side of the recipient to keep the collecting system and ureter medial. Thus, if the ureter needs to be reimplanted because of distal obstruction, or if the entire structure becomes necrotic, the bladder can be anastomosed directly to the renal pelvis, an impossibility if these structures are on the organ's lateral side. Alternatively, if the kidney must be placed on the ipsilateral side of the recipient, the ureter may be curved gently back upon itself to enter the bladder (Figure 1).

The rectus sheath is opened and the rectus muscle transected at its insertion, taking care to ligate and divide the inferior epigastric vessels; occasionally a length of inferior epigastric artery may be used to vascularize a polar branch of the kidney. The oblique muscles are opened appropriately. The retroperitoneal iliac space is then entered by reflecting the peritoneum and its contents medial and cephalad. In the male, the vas deferens is dissected and retracted medially;

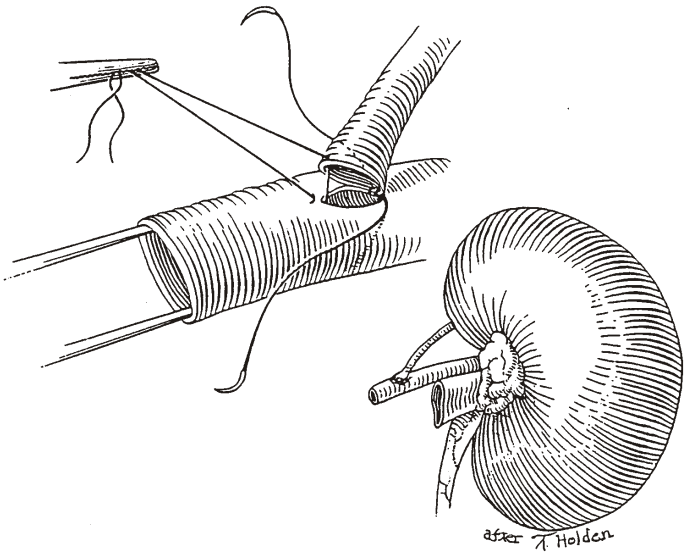

Figure 2. Small polar arteries can be anastomosed end-to-side to the main renal artery on a back table under optimal conditions. The kidney can then be transplanted with a single artery. As many as four polar branches have been successfully anastomosed in this manner. (with permission of WB Saunders, Philadelphia)

if this structure is divided, there is a high incidence of later hydrocele. In females, the round ligament is sacrificed. The iliac vessels are isolated from the surrounding fat and lymphatics. Large lymph nodes are usually removed to facilitate exposure of the iliac vein; all lymphatic-bearing perivascular tissues are carefully ligated or clipped to prevent lymph leaks or eventual lymphocele formation. The external iliac vessels are then isolated between the inguinal ligament and the hypogastric artery. Lumber veins which may enter the dorsal surface of the iliac vein should be carefully isolated and clipped or ligated in situ, as these fragile structures can tear and retract into the pelvis where their bleeding may be difficult to control. The dome of the bladder is identified and a portion freed from surrounding fat, a maneuver made considerably easier because of the retained bladder irrigant.

Vessels

Once the iliac space of the recipient is prepared, the kidney, which itself has been dissected free from surrounding perinephric fat, can be transplanted. Although earlier surgeons (and still a few current ones) used an end-to-end anastomosis between recipient hypogastric artery and donor renal artery, more usually the renal vessels are joined end-to-side to the iliac vessels at a convenient distal location in the pelvis. Indeed, the incidence of later renal artery stenosis was considerably higher when end-to-end anastomoses were performed [18]; such a complication has become exceedingly rare using the easier and faster technique of end-to-side anastomosis. The isolated vessels are clamped and appropriate longitudinal incisions made in them. Systemic heparinization is not necessary although the isolated iliac segments must be washed completely free of blood and clot during the creation of the arterial and venous anastomoses. The renal vessels are anasto-

mosed in sequence using continuous monofilament suture. Occasionally, the depth of the iliac space may make it difficult to visualize adequately the lateral side of the venous anastomosis; in this case, the lateral walls of renal vein and iliac vein can be sutured from the inside first, followed by the medial walls.

Because renal arteries are end arteries that supply discrete portions of parenchyma, it is crucial that technically perfect anastomoses be created with host vessels. A tiny branch can occasionally be sacrificed, particularly if it lies on the upper pole and the resulting infarct appears inconsequential. If the kidney is from a cadaver donor, it is often convenient to fashion a small aortic patch surrounding the renal artery orifice that can be anastomosed directly to iliac artery; this is particularly helpful if the renal vessel is small or fragile. However, if the artery is unduly long, it must be amputated to an appropriate length so that it will not kink when the graft is positioned in the iliac space. It is usually convenient to include multiple renal arteries in a single aortic patch if they are relatively close together, or use two separate patches if they lie apart. The ends of two equal-sized donor arteries may be fashioned together to create a single large orifice. It is most important to retain small lower pole arteries, as they are often the sole blood supply for the renal pelvis and ureter. Often such polar arteries can be anastomosed end-to-side to the main renal artery at a back table under optimal light and positioning before the kidney, now with a single artery, is implanted (Figure 2). Alternately, the inferior epigastric artery of the recipient may be joined end-to-end to the polar branch. In contrast, if there are two renal veins, the smaller one may usually be ligated with impunity. In general, with good technique, both short- and long-term outcomes are similar in grafts with multiple arterial anastomoses compared to those with a single one [19].

Ureter

For many years, the Leadbetter-Politano method of retaining a long length of donor ureter to implant near the recipient trigone via cystotomy was used. This method was extremely useful in re-implanting the relatively undissected native ureters into the patient's own bladder, particularly as they retain much of their relatively diffuse blood supply. However, in a renal transplant where the entire ureter is dependent upon a small ureteric arterial branch from the renal artery, use of a long ureter may be problematic: the potential threat of important sequelae including arterial thrombosis and ureteral infarction is ever present and the overall incidence of ureteric complications in transplant patients using this method has been about 15% [20]. In addition, bladder dehiscence at the cystotomy site was not rare, presumably because of the non-healing effects of steroids. Since the institution of the Lich-Gregoire technique of implanting a short length of donor ureter directly onto a small cystotomy made in the bladder dome, however, the incidence of ureteric complications has dropped to < 5% – an important technical improvement [21]. By closing the muscle layers of the bladder over a short length of distal ureter, one can create an anti-reflux valve. Although reflux is often seen in radiocontrast studies of transplanted kidneys, it appears to have little clinical significance. Approximated double ureters, an occasional normal anatomical variant, are implanted closely together into the bladder dome and the muscular tunnel made to include both. However, if the ureters lie far apart or come from separate collecting systems, they are implanted into the bladder individually. Stents are not used. Although some surgeons still advocate direct anastomosis between donor and recipient ureter, this tech-

nique entails removal of the ipsilateral native kidney, a procedure that enlarges the entire operation and is probably not advantageous.

On occasion, use of the recipient bladder may be problematic. If the bladder is shrunken from years of disuse, it can be dilated before transplantation by intermittent installation of urological solution; bladder dynamics should be assessed preoperatively. Patients who are paraplegic or have an atonic bladder because of myelomeningocele may present with an ileal conduit already in place. Rarely, if the bladder cannot be used, an ideal conduit should be created before the transplant, allowed to mature and then, at the time of engraftment, the donor ureter can be implanted into it. It is helpful technically to place a Foley catheter into the conduit via its stoma and inflate its balloon so that the appropriate bowel loop can be identified during laparotomy. The ureter is anastomosed directly to the bowel using fine sutures.

Following completion of the transplant, the kidney should be placed gently into the retroperitoneal space. Upon occasion, it will have to be positioned carefully to ensure optimal arterial flow; it is critical that the cortex is pink and well-perfused as the incision is closed. Muscles and fascia are then re-approximated with running monofilament sutures and the remainder of the wound repaired routinely. In contrast to the technique used in children, only rarely is the transplanted kidney placed intraperitoneally in adults – usually in the context of iliac spaces that have already been used. In general, for re-transplantation, we have found it easier to remove the old kidney, dissect out the iliac vessels and recreate the retroperitoneal space. All iliac incisions are drained postoperatively of blood or serum using closed suction drains; drainage usually stops within 36 hours and the drains can be removed. Occasionally, if a lymph leak is prolonged, the closed system drain may be left in place for relatively prolonged periods and the patient taught to empty it appropriately at home.

Occasionally, it is necessary to re-explore the transplanted kidney due to hemorrhage, urine leak, or other complications. If there is a possibility of salvaging the transplant, the donor kidney should be isolated carefully with its capsule intact because intracapsular bleeding is diffuse, difficult to control, and may preclude isolation of the ureter or vessels. If the entire organ needs to be removed – especially after healing has occurred – it is easier to enter the capsule and dissect out the kidney and vascular pedicle intracapsularly. One can then clamp, divide and suture-ligate the pedicle in bulk prior to removing the kidney.

Postoperative Care

The majority of allografts both from living-related sources and from many cadaveric donors begin to produce urine immediately after revascularization. Some may diurese large volumes, i.e. 1,000 ml/hour, due to multiple factors including fluid overload, osmotic diuresis, use of intraoperative diuretics and transient proximal tubule concentrating defects. Although diuresis gradually tends to normalize over the first 24 – 72 hours and oral intake resumes, appropriate IV fluid replacement is necessary in the interim. The output should be replaced volume for volume with cystalloid in the first several hours (at a minimum of 100 ml/hour). Because of its potassium (K+) content, Ringer's lactate should probably not be used if the kidney is not fully functioning. Commonly, the patient may diurese a substantial volume for the first 12 hours or so followed by a rapid reduction in output to low levels. In most cases, fluid boluses will restore adequate urine output.

Once hourly output has normalized, replacement can be given as in a normal postoperative patient – based on the previous hour's output or 30 ml/hour, whichever is greater. With very sick patients, adjustments can be made based on CVP or other monitoring techniques. Serial determinations of serum and urine electrolytes can guide adequate correction. Despite the usual brisk early diuresis, K+ requirements are usually minimal.

In allografts with delayed function, cell lysis secondary to surgical dissection and the use of blood transfusions may produce a sudden rise in serum K+ levels. Electrocardiographic changes in the face of hyperkalemia demand prompt treatment. Intravenous administration of calcium gluconate can rapidly reverse the cardioplegic effects of hyperkalemia. Injection of glucose/insulin or bicarbonate drives K+ intracellularly. Potassium exchange resin (Kayexalate) enemas with water may remove an unpredictable amount of K+ over time; however, these resins may also form significant colonic concretions. Oral administration of ion exchange resins plus sorbitol is the preferred method. Sorbitol should not be given per rectum because it has been associated with bowel perforations [22]. These interventions are only temporizing measures that are used prior to reinstitution of dialysis until graft function returns.

Postoperative ileus is usually transient because the peritoneal cavity is violated infrequently. Oral intake can usually be re-instituted on postoperative Day 1 or 2. Once adequate oral intake resumes intravenous fluid replacement is discontinued, as restoration of the normal thirst mechanism is the best guide to the state of hydration.

Postoperative Mechanical Complications

Both mechanical and non-mechanical complications (see Chapters III-5, 6 and 7) may produce primary anuria or deteriorating function in grafts that have achieved an initial diuresis. Diagnosing the cause of graft dysfunction is one of the most challenging aspects of the care of the transplant recipient and should be based on careful integration of information obtained through clinical evaluation, laboratory tests, imaging studies and biopsy results. Accurate diagnosis is critical because reversal by rapid identification and appropriate treatment is usually possible. If poor function is thought to be due to ATN or unrecognized rejection, a renal biopsy may be diagnostic. Renal ultrasound may detect the majority of mechanical abnormalities and is a convenient, non-invasive modality that should be used as often as necessary to diagnose and follow the problem [23].

Perinephric Infections

The incidence of wound and perinephric infections was striking in the earlier years of transplantation due to inadequate diagnosis, lack of ultrasound, less aggressive re-exploration of structural abnormalities or fluid collections, and over-aggressive immunosuppression. The administration of a single bolus of high-dose broad spectrum antibiotics [24] during anesthesia induction has reduced the overall incidence of wound sepsis dramatically in recent years to as low as 1% in some studies [25]. Prevention of postoperative infection is critical in this population because of the administration of powerful immunosup-

pressive agents at the time of the renal transplant procedure and because fluid collections may occur in the retroperitoneal space despite meticulous technique [26]. Urinary tract infections (UTI) have been associated with wound infection [27]. The diagnosis of perinephric infections in particular may be difficult as they are deep and symptoms and signs are often masked by the anti-inflammatory properties of steroids (Chapter III-6). Perinephric collections of blood, urine, or lymph should always be suspected in the postoperative period, identified by ultrasound, and treated promptly. Advances in interventional radiology allow most fluid collections to be corrected with percutaneous drainage and placement of a catheter for persistent collections. If the fluid collections are not amenable to percutaneous drainage or there is an extensive hematoma, operative re-exploration for drainage or clot removal becomes necessary because these collections serve as a nidus for infection and eventual development of perinephric abscesses.

Acute Hemorrhage

Bleeding may arise from any part of the graft site in the early postoperative period. The most serious source may be from one of the vascular anastomoses, or from a small branch of the renal artery unnoticed at the time of removal from the donor or implantation into the recipient. Commonly, no discrete source of bleeding can be found on re-exploration despite careful examination of the entire kidney and renal bed. The clot is removed, the field irrigated and the entire transplant and retroperitoneal space carefully examined for suspicious sites. If the drain has been removed, it is best to replace it with a new one.

On rare occasions, while undergoing a fulminant, irreversible rejection episode despite strenuous immunosuppressive measures, the renal allograft may enlarge rapidly and rupture. This catastrophe often presents as acute perinephric hemorrhage with obvious wound swelling and severe pain localized to the transplant site or referred to the back or rectum. Hypotension occurs infrequently as the retroperitoneal hemorrhage is relatively contained. Upon exploration, it is important for the surgeon to reach cephalad along the psoas gutter to remove the large clots that often accumulate there. External rupture extends through the cortex and capsule. On occasion, the rupture may involve either the collecting system or renal pelvis, resulting in severe hematuria or sudden anuria from clots in the renal pelvis. Transplant nephrectomy is almost invariably indicated, as it is rare to salvage organs that are so vehemently rejected. Even if the rupture can be repaired with mass sutures on pledgets, the organ usually undergoes complete immunological destruction.

The presence of hematuria in the postoperative period may depend upon the method of ureteral implantation. Direct anastomosis of the ureter to the bladder dome avoids a cystotomy and the blind creation of a submucosal tunnel, as advocated by Leadbetter and Politano [20]. A comparison of the Leadbetter/Politano and the stented extra-vesical techniques of ureterovesical anastomosis demonstrated a clear reduction of clinically significant hematuria with the latter method [21]. Minor hematuria may be common in the first few hours or days after engraftment despite cauterization of the tip of the ureteric artery at time of implantation and may also occur from the small cystotomy incision. Although this type of bleeding usually ceases spontaneously, it may occasionally be severe enough to obstruct the catheter with clot. Gentle intermittent irrigation of the urinary

catheter should be performed initially in all patients who are anuric postoperatively to rule out obstruction of the catheter tip. It may be necessary to change the catheter when there is a ball-valve effect, allowing free irrigation, but no drainage. When large clots form in the bladder a 3-way irrigation catheter may be employed to dissolve them; it is often more efficacious to remove the catheter and allow the patients to evacuate them spontaneously; after a few days clots will begin to break up due to the activity of urine urokinase.

Hemorrhage into the collecting system with secondary clot retention may occur after needle biopsy of the allograft. If hematuria is severe, and clots obstruct the renal pelvis, a percutaneous nephrostomy tube may be placed under ultrasound guidance to divert urine flow until the clots lyse. Unremitting bleeding in this setting may occasionally be controlled by selective embolization via arteriography. Rarely, an arteriovenous fistula may form within the renal parenchyma; if this cannot be clotted angiographically, transplant nephrectomy may become necessary.

Late Vascular Complications

Multiple renal arteries are present in about 20% of kidneys. As some polar arteries are small, inadequate flow leading to thrombosis may produce segmental renal infarcts; if this occurs in the lower pole, the ureter or collecting system may become involved. If a pole infarcts without involving the renal pelvis or ureter, the kidney may be saved by excising the necrotic portion back to viable tissue and closing the open area with large bulk sutures on Teflon pledgets, thus avoiding tearing of the cortex. Surgery should be aggressive and definitive; calyceal-cutaneous fistulae, resulting from a polar infarct never heal, may become infected and are often fatal. If the pelvis is infected, the organ may be salvaged – if the organ has been placed in the contralateral side of the recipient – by joining the bladder directly to the kidney capsule and leaving a large nephrostomy tube in place for several weeks.

Vascular thrombosis is an uncommon early complication in adults, although it may occur more commonly in pediatric transplantation where it has been associated with CyA use. Although arterial thromboses may rarely occur spontaneously, independent of rejection and without an obvious cause, they more likely develop secondary to an imperfect anastomosis or unrecognized intimal flap in the donor vessel. This latter abnormality occurs more commonly in kidneys from living sources. At the same time, the surgeon should be aware of the very delicate and poorly anchored intima often seen in the iliac arteries of diabetic recipients. In these instances impeccable vascular surgical technique is essential. The incidence of venous thrombosis varies between 1% and 4%, and usually occurs when the graft is placed into an inappropriately tight retroperitoneal pocket [28]. In either instance, graft prognosis is poor and transplant nephrectomy is invariably necessary, as corrective surgery (no matter how prompt) cannot salvage such organs.

Before the use of an aortic patch became routine, and particularly when the renal artery was anastomosed end-to-end to the hypogastric artery, the development of renal artery stenosis years after engraftment was rather common, with a incidence ranging from 3 – 10% of all transplant recipients [18, 29]. More recently, experience has been gained with percutaneous transluminal angioplasty (PTA), a technique that carries less morbidity

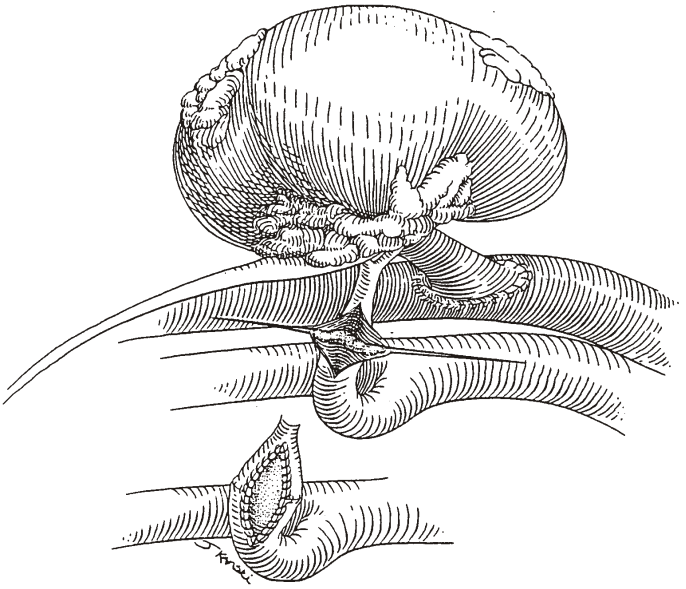

Figure 3. Renal arteries with localized stenoses at the original anastomosis with the recipient hypogastric artery can be patched open with small pieces of vein. (with permission of WB Saunders, Philadelphia)

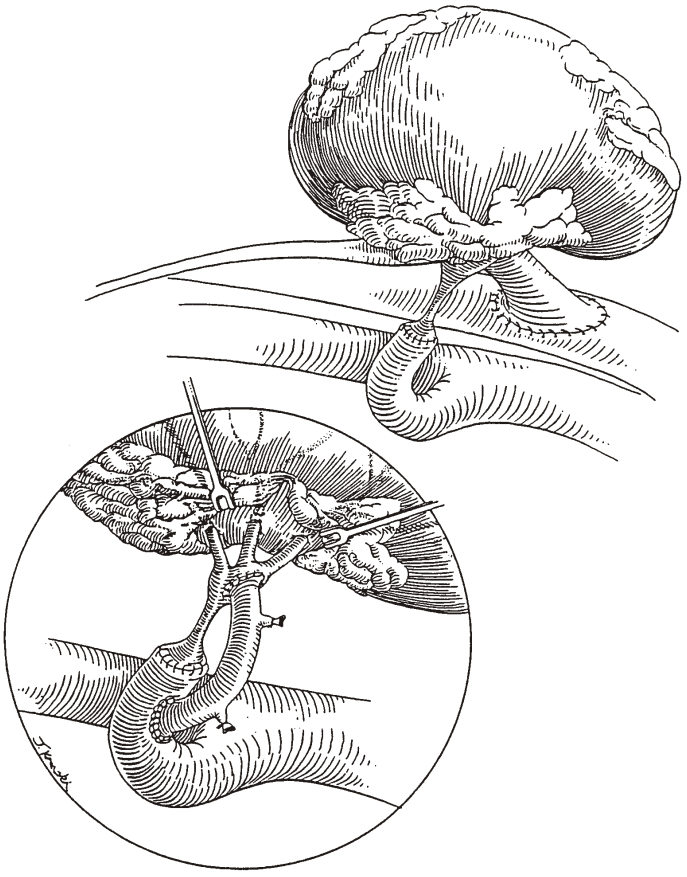

Figure 4. A long stenosis can be bypassed with a segment of vein placed between the recipient hypogastric artery and the post-stenotic dilated portion of the renal artery. (with permission of WB Saunders, Philadelphia)

than direct surgical repair, especially when the anastomotic stenosis is recent, linear and proximal [30]. Although late stenoses are probably best treated surgically by vein patches or bypass as intense fibrosis often prevents adequate dilatation (Figures 3 and 4), radiological treatment may be a reasonable first step, depending on the expertise of the individual institution. Improved imaging techniques with color-flow Doppler have also allowed better assessment of the hemodynamic significance of arterial stenoses [31].

With more elderly recipients, arteriosclerosis of the aortoiliac system becomes a more frequent problem for the transplant surgeon. Possible sequelae include reduced blood flow to the allografted kidney, secondary hypertension and atheromatous emboli. Aortic replacement, usually for aneurysms, has generally been successful in recipients of renal allografts; the majority of grafts tolerate the clamp time without bypass and resume full function immediately or within a few days after reconstitution of the blood supply. Overall prompt diagnosis and aggressive treatment of vascular abnormalities developing after transplantation have salvaged many kidneys that hitherto would have been lost.

Urine Leak

Despite technical improvements, the ureterovesical anastomosis remains the most likely site for postoperative complications following renal transplantation. Urine leak at the bladder anastomosis or mechanical obstruction of the ureter occurs most commonly in the early postoperative period. Leak usually develops from necrosis of the distal ureter due to an inadequate blood supply (secondary to either thrombosis of or damage to the ureteric artery, the sole blood supply to the graft ureter). Urine leak happens more frequently in kidneys with multiple renal arteries and in living-related allografts when exposure may be limited during donor nephrectomy and the ureter stripped of its periureteric vessels in the surrounding fat. As noted, the shortest practical length of ureter should be utilized during engraftment to preserve maximum blood supply. Meticulous microvascular anastomosis of polar branches may decrease the occurrence of this complication. Urinary leak may also result from technical errors, infection or clot retention leading to acute bladder distension and disruption of the ureterovesical anastomosis.

The clinical signs of urine leak resemble those of graft rejection or obstruction by lymphocele or hematoma and may include unexplained fever or graft tenderness, and increased wound drainage. Swelling of the scrotum, labia or thigh ipsilateral to the graft is virtually pathognomonic of leak. If a drain is in place, the presence of blue fluid after intravenous administration of trypan blue (which is excreted in the urine turning it dark blue in color) is diagnostic. Alternatively, the origins of a fluid collection or drainage can be diagnosed by the simultaneous measurement and comparison of creatinine concentration in the urine, serum and drainage fluid. Serum and lymph have equal creatinine concentrations while that in the urine is usually considerably higher. Although urine output may diminish abruptly, dramatic changes in volume do not necessarily occur as a leak develops; a necrosed ureter may still act as a conduit for several days before the condition becomes obvious. More commonly, renal function progressively declines after several days of satisfactory function. Ultrasound can demonstrate a perinephric fluid collection that may be aspirated to determine creatinine concentration for comparison with serum and urine. Rarely,

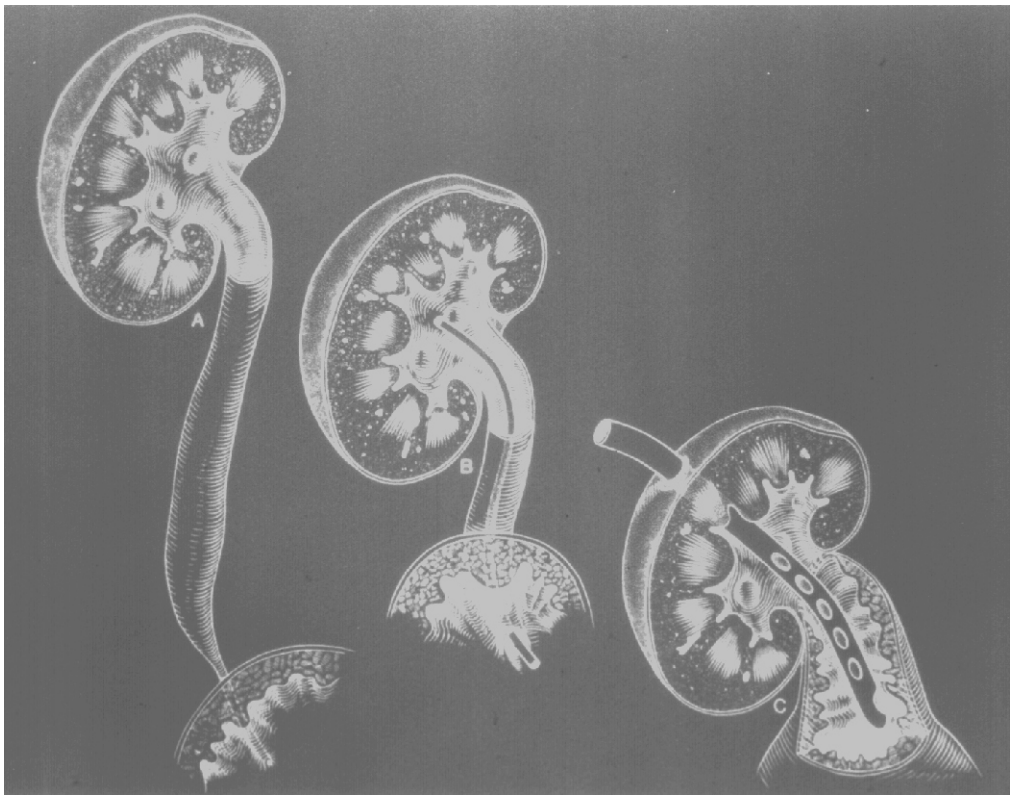

Figure 5. If the distal ureter becomes stenotic, the affected area can be removed and the ureter reimplanted into the bladder. If the ureter and collecting system necrose, the bladder can be anastomosed directly to the kidney capsule and protected by a nephrostomy tube for several weeks. (with permission of WB Saunders, Philadelphia)

there is re-absorption of the leak into the peritoneal cavity. When a hole is inadvertently made in the peritoneum during the transplant procedure, a urine leak can result in the development of urinary ascites. Definitive diagnosis, localization, and temporary diversion of a urine leak can be made by ultrasound-guided placement of a percutaneous nephrostomy tube. Decompression and external drainage for 2 – 3 days allow normalization of graft function and ensures optimal condition of the patient at re-operation. As spontaneous closure is unlikely unless the leak is minimal, surgical correction is usually indicated [32]. Retrograde cannulation is extremely difficult due to the location of the transplant ureteral orifice and is rarely attempted. An internal stent placed percutaneously under ultrasound guidance between renal pelvis and bladder via the repaired ureteroneocystostomy is sometimes used; this technique can significantly reduce the incidence of infections compared to retained external nephrostomy tubes [33].

Ureteral Obstruction

In the immediate postoperative period, ureteral obstruction most likely results from technical error, a ureteral twist, or an obstruction within an overtight muscular tunnel – edema should not be considered a reason to delay re-exploration. Within a few days of transplantation, ureteral narrowing from ischemia, local infarction or, less commonly, adhesions may occur and can be associated with rejection [34]. Stenosis appearing weeks or months after transplantation manifests as slow functional deterioration of the allograft. A markedly dilated ureter or collecting system may be seen on ultrasound. As this technique may occasionally fail to demonstrate dilatation, percutaneous nephrostomy with antegrade pyelography is a more definitive diagnostic procedure; localization of the obstruction is of great help at reparative operation. It should be emphasized, however, that mild dilatation of the ureter and collecting system is a normal finding in kidneys after transplantation.

Although percutaneous transluminal ureteral dilatation can correct ureteral obstruction (at least over the short-term) the long-term efficacy of this technique is in doubt and continued close monitoring of anatomical and functional results remain mandatory. Success appears to be related to the timing of stenosis development with better results achieved in stenoses that develop within the first three months of transplantation [35].

When surgical repair becomes necessary, the original incision is re-opened, and the lower pole of the graft mobilized. The surgeon should take care to keep the plane of dissection outside the kidney capsule to minimize bleeding from the renal cortex. As the ureter may be exceedingly difficult to locate at re-exploration, a transuretheral catheter, placed percutaneously via ultrasound, may be of immeasurable value in identification. The ureter and bladder dome are isolated and the distal ureter divided and re-implanted (Figure 5). If the remaining ureter is too short for this purpose, the bladder can be mobilized cephalad and directly anastomosed to the renal pelvis.

Lymphocele

Lymphocele develops most commonly from leakage of pelvic lymphatic vessels injured or transected during exposure of the iliac vessels or, more rarely, from the renal surface. The incidence of lymphocele can be significantly reduced by meticulous ligation of pelvic lymphatics during the exposure of iliac vessels [36]. The lymph drains into the retroperitoneal space where it may form extensive collections associated with lower abdominal swelling, tenderness and deterioration of graft function, probably due to external pressure on the graft or ureter. On occasion, lymph output may be severe and intractable enough to enter the peritoneal space and produce ascites. As noted previously, ultrasound- or computed tomography (CT)-guided aspiration can differentiate lymph from urine or hematoma, by comparing the creatinine concentration in the respective fluids. Percutaneous drainage or marsupialization of the lymphocele into the peritoneal cavity is often effective. Marsupialization can be performed with either open or laparoscopic techniques [37].

Summary

Refinements in operative technique and improved perioperative care have markedly decreased the incidence of complications after renal transplantation. With meticulous perioperative care and careful attention to detail, even better results can be achieved. But, as donors become less ideal (older, diabetic, etc.) in an attempt to expand the donor pool, we still must guard against potential mechanical problems and strive to identify and aggressively treat postoperative complications.

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Induction and Maintenance Immunosuppressive Therapy in Renal Transplant Recipients

Richard M. Lewis

"Induction" vs. "Maintenance" Therapy: Operational Definitions

Introduction

Characterization of the "homograft reaction" by Sir Peter Medawar and his contemporaries during the 1940s and early 1950s established the scientific foundation underlying the rational use of immunosuppressive therapy in renal transplant recipients. These time-honored, fundamental precepts of transplantation biology also provide a conceptual basis for the formulation of working definitions of the terms "induction" and "maintenance" as they apply to contemporary clinical practice. Particularly relevant axioms are summarized in the following excerpts from Medawar's Croonian lecture [112]:

- "The homograft reaction . . . is immunological in character [and] put into effect by activated lymphoid cells . . . It is natural to think of the large or small lymphocyte as the effector of the reactions."
- "A regional graft . . . will 'activate' the regional lymphnodes, in which there occur the histological changes now known to be associated with an immunological response."
- "It seems to be a regular property of these 'cellular immunities' that they manifest themselves in the guinea pig and man by dermal hypersensitivity reactions of the delayed type."
- "There is a latent period before the inception of the homograft reaction. . . . With skin homografts much of the latent period is presumably occupied with making vascular connexions, for the sensitivity produced by intraperitoneal injections of splenic cells or of cell-free antigens comes into force with remarkable speed."
- ". . . the least equivocal measurement of the strength of transplantation immunity is the survival time of the homograft against which it is directed: the stronger the reaction, the more quickly will the homograft die."
- "The rejection of a homograft leaves its host in a . . . sensitive state as a consequence of which a second homograft transplanted on some later occasion from the same donor is destroyed more quickly than one which preceded it."

Relatively straightforward, operational definitions of the terms "induction" and

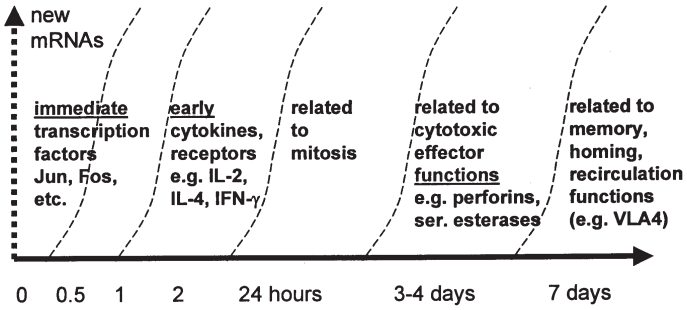

Figure 1. Time Course of Gene Expression Following T Cell Activation [21].

"maintenance" follow from these fundamental precepts. Specifically, the phrase "induction" therapy may be designated to refer to treatment directed at abrogating the relatively acute process involved in transitioning the host's immune system from a state of nonsensitization to one of acquired, allospecific immunity. A schematic profile of the particular mechanisms involved in the de novo acquisition of donor-specific immunity, as depicted by Campbell and Halloran [21], is shown in Figure 1. In contrast to the operational concept of "induction" as outlined above, the objective of "maintenance" therapy may be defined as sustaining the allospecific immune response in a state sufficiently weakened so as to preclude immunologic graft loss without resulting in a prohibitive clinical risk vis-a-vis host morbidity and mortality.

Induction and Maintenance Agents: Fundamental Characteristics

It is self-evident that the particular suitability of individual drugs for use as induction and/or maintenance agents derives from their mechanism(s) of action, toxicity profiles, and pharmacologic properties. High-dose steroids and antilymphocyte antibody preparations represent classical induction agents in that they exert an immediate and intense suppressive effect during the period of acquisition of allospecific immunity and are characterized by a relatively invariant dose-response relationship. In addition, the adverse effect profiles, requirement for parenteral administration, and costs of these agents clearly limit their use to a relatively short period of time. In contrast, contemporary maintenance agents exert a relatively weaker and more selective suppression of the immune system, mitigate events that occur at intermediate phases of the cell cycle, and are characterized by highly variable dose-response relationships. An oral route of administration and clinically acceptable therapeutic indices associated with long-term use render these drugs more optimally suitable for use in maintenance therapy.

The remainder of the present chapter will focus on benefits and pitfalls associated with each of the principle agents currently available for general use as induction and maintenance immunosuppressive options. A brief review of the relatively limited data available to date regarding clinical use of sirolimus, an inhibitor of the late phase of T cell activation, and humanized monoclonal antibodies directed against the interleukin-2 receptor Il-2R will also be presented.

Corticosteroids

Background

Corticosteroids exert their immunosuppressive effects via multiple mechanisms that are dose dependent and encompass acute lymphocyte depletion in regional and central lymphoid tissue as well as inhibition of cytokine gene transcription essential to the T cell activation phase of the alloimmune response [13, 14, 30, 53, 64, 112]. The clinical science underlying the use of steroids for the prevention and treatment of renal allograft rejection originated with Addison's observation that adrenal insufficiency was associated with lymphoid hyperplasia [30]. In 1945, Dougherty and White [30] described an acute "disintegration" of lymphocytes within the thymus, spleen, and peripheral nodes detectable as early as 3 hours following a single injection of exogenous adrenocorticotropic hormone (ACTH) or adrenal cortical extract. Lymphocytes developed pyknotic nuclear changes reminiscent of those currently associated with programmed cell death, lymph nodes became edematous, and germinal centers disappeared [30]. This process of lymphocyte dissolution was rapidly reversible with a completely normal histologic appearance restored to lymphoid tissue in the mouse model at 24 – 36 hours [30].

Hume [68] initially utilized ACTH and corticosteroids during the early 1950s in unsuccessful attempts to abrogate acute renal allograft rejection in the clinical setting. Histologic and functional reversal of an early, severe acute rejection episode in response to a prohibitively toxic dose of corticosteroids was first described by Goodwin et al. [42]. Starzl, Hume, and Merrill subsequently reported successful clinical outcomes following renal allotransplantation by combining use of the purine synthesis inhibitor, azathioprine (Aza), with large doses of steroids during the immediate post-transplant period and relatively low doses thereafter [69, 114, 161]. The rationale for use of higher doses of corticosteroids to abrogate the induction phase of the homograft reaction was affirmed by Hayry et al. [59] in a prospective trial comparing postoperative administration of methylprednisolone at doses of 1.0 vs. 3.5 mg/kg/day. Serial fine-needle aspiration biopsies and aspiration cytologies demonstrated delayed onset and reduced severity of early post-transplant graft infiltration in association with the high-dose induction regimen [59]. Consistent with these histologic findings, acute rejection episodes were less severe and more responsive to therapy while one year graft survival was 24% higher in the high-dose induction cohort [59].

Contemporary Clinical Issues

The timeless quandary posed by the use of corticosteroids in renal transplantation derives from the contrast between their striking efficacy in abrogating the "homograft reaction" and the formidable side effects associated with use of large cumulative doses. The latter are well-known and include morbid weight gain, glucose intolerance, hypertension, hyperlipidemia, atherosclerotic cardiovascular disease, acne, avascular necrosis of the femoral head, opportunistic infections, peptic ulcer disease, and Cushingoid deformities. The remainder of the present section will review results of clinical studies assessing the benefits and disadvantages of the following approaches to minimizing morbidity attendant to cumulative steroid exposure:

– reducing acute rejection rates,
– utilization of antilymphocyte preparations as first-line treatment for acute rejection,
– steroid avoidance,
– steroid withdrawal, and
– alternate day steroid regimens.

Given the prevalence of bolus steroid therapy as first-line treatment for acute rejection episodes, the most significant advance in reducing morbidity consequent to high cumulative doses was the introduction of cyclosporine (CsA) which was associated with a reduction in the normative incidence of acute rejection from a rate > 80% to an average of 40 – 50% [47a, 58, 90, 106b, 110, 151, 164]. While representing substantial progress, the latter figure was not inconsequential, however, as most first acute rejection episodes in the CsA era continued to be treated with a short course of bolus steroid therapy not infrequently followed by a relatively high oral dose tapered over an extended period of time. Moreover, recurrent rejections occurred with a frequency of ≥ 15% and were also not uncommonly treated with high dose steroid therapy. Encouragingly, progress is currently being made in the quest to reduce acute rejection rates even further. Contemporary approaches associated with rejection rates ≤ 25% have included "fine-tuning" induction and maintenance therapy by combining antilymphocyte antibody therapy during induction with careful attention to cyclosporine drug exposure during the early post-transplant period as well as increasing net immunosuppression by substituting mycophenolate mofetil (MMF) for Aza in CsA-based regimens and/or and substituting tacrolimus (FK506) for CsA (see below). One additional approach to minimizing cumulative steroid exposure is the use of antilymphocyte preparations as first-line therapy for the treatment of acute rejection. Data providing perspective on the benefits and risks of this strategy have been reviewed by Hricik [64, 65].

Steroid Avoidance and Withdrawal Strategies: Impact on Efficacy

With regard to "steroid-free" immunosuppression, the reader is referred to Hricik's meta-analysis of the 7 randomized prospective trials undertaken through 1993 [65]. Four "steroid avoidance" studies compared cohorts of patients receiving CsA monotherapy vs. CsA and Prednison (Pred) or CsA-Aza-Pred. Results have been inconsistent. Both one year graft survival and acute rejection rates in the steroid-free cohorts ranged from 20% lower to 50% higher than those occurring in steroid-treated controls [65]. Steroid withdrawal, carried out between 6 days and 6 months following transplantation, was evaluated in 3 studies [65]. Graft survivals were 3 – 5% lower and acute rejection rates 18 – 35% higher in patients withdrawn from steroid therapy vs. controls [65]. Combining the data from all 7 studies, steroid-free immunosuppression was assessed as successful in 323/681 patients (47%), a figure similar to that reported in the pediatric population by Tejani et al. [167]. In contrast, an uncontrolled, single center study by Hricik et al. [67] reported a 79% success rate in a cohort of 75 patients withdrawn from steroids ≥ 6 months following transplantation. All had stable creatinines < 2.5 mg /dL at the time of withdrawal [67]. While 80% of the patients remained steroid-free at 18 months following withdrawal, 22/75 received 38 courses of pulse steroid therapy for the treatment of acute rejection, and 16/22 received a second course of bolus steroid therapy for recurrent acute rejection. Two grafts were lost

despite attempts at rescue with the monoclonal antibody OKT3 [67].

To date, the literature does not permit definitive inferences regarding the risks vs. benefits of routine conversion to an alternate-day steroid regimen following renal transplantation [31, 64]. One controlled trial from the Aza-Pred era found a beneficial impact on risks of two complications that have, fortunately, occurred with substantially lower frequency over the past decade, namely, peptic ulcer disease and avascular necrosis of the hip. Hypertension, weight gain, and hyperlipidemia remained problematic in this series, however [31].

Steroid Avoidance and Withdrawal Strategies: Risks vs. Benefits

One practical limitation implicit in the results of all of the abovementioned studies is the absence of a consistently reliable clinical method for determining an individual patient's risk of acute immunologic injury following steroid withdrawal. To date, immunologic monitoring has not provided a reliable basis for predicting acute rejection following steroid withdrawal in recipients of cadaveric allografts. Kerman et al. [88] have reported encouraging short-term results in haploidentical living donor transplant recipients, however, using donor-specific hyporesponsiveness assessed at one year by mixed lymphocyte culture.

Another important concern related to steroid avoidance or withdrawal is a potentially adverse impact on long-term graft loss due to chronic arteriopathic and/or glomerulopathic processes. In a prospective, controlled trial from Canada published in 1992, steroid withdrawal in a group of patients receiving a dual Pred-CsA maintenance regimen did not appear to impact on adversely on graft survival for 5 years [155]. Thereafter, however, the rate of graft loss in the steroid-free cohort was significantly increased vs. controls [155]. Unfortunately, specific causes of graft failure were not detailed in this study. Nonetheless, the data clearly suggest that short-term, acute rejection is not the only important risk that must be accounted for in considering the issue of steroid-free immunosuppressive therapy.

Metabolic studies also support a cautious approach to the issue of withdrawing steroids 6 – 12 months following transplantation. While it is clear that late steroid withdrawal reduces glucose intolerance in renal transplant recipients, the beneficial impact on other metabolic abnormalities is less straightforward. Both total cholesterol and high density lipoprotein (HDL) levels were found by Hricik et al. [66] to be reduced following steroid withdrawal. Total cholesterol to HDL ratios were unchanged in diabetics and increased in nondiabetics [66]. These observations prompted the conclusion that "it is premature to presume that withdrawal of steroid therapy will reduce the cardiovascular risk related to hyperlipidemia in cyclosporine-treated kidney or kidney-pancreas transplant recipients" [66].

Summary

Corticosteroids have remained an indispensable element in the immunosuppressive armamentarium despite their adverse effects. Morbidity related to cumulative exposure was significantly reduced, however, following the introduction of cyclosporine and further abrogated by the development of contemporary infectious and peptic ulcer prophylaxis regimens. While steroids may be withdrawn with-

out adverse short-term sequelae in just under one-half of CsA-treated renal transplant recipients, current immunologic monitoring methods do not permit a priori identification of individuals who will tolerate withdrawal on both a short- and long-term basis. Moreover, population studies have suggested that steroid withdrawal may predispose to long-term graft failure while the benefits accruing to changes in lipoprotein profiles are equivocal.

Given that long-term outcomes associated with Cyclosporine (or FK506)-based, steroid-inclusive maintenance regimens have improved to the point of establishing a formidable gold standard (reviewed below), it is arguable that determining if the rate of reduction of steroid dose during the early post transplant period may be safely accelerated represents a more compelling priority than that of complete withdrawal after reaching doses of 7.5 – 10 mg/day. Nonetheless, clinical trials evaluating the impact of steroid withdrawal as early as one week following transplantation on acute rejection rates and one year outcomes have been initiated in studies involving use of one or more of the new era xenobiotic agents, FK506, MMF, the micro-emulsion formulation of CsA (CsA-ME), and sirolimus. Until more data are forthcoming, however, unconventional approaches to steroid tapering, routine use of alternate-day therapy, and consideration for withdrawal can be generally advocated only in the context of formal trials or appropriately individualized clinical circumstances.

Antilymphocyte Preparations

Introduction

A compelling mechanistic rationale for the use of antilymphocyte antibodies as induction agents was established by both early preclinical and clinical studies [1, 182, 188, 119, 120, 98]. Heterologous anti-sera were first used at the turn of the century as research tools for elucidating the role of individual cell types in various immunological phenomena by eliminating them from the experimental milieu [36]. In 1961, Waksman et al. [182] reported that the administration of rabbit anti-guinea pig lymphocyte sera abrogated the tuberculin reaction in guinea pigs and delayed the onset and severity of rejection of skin grafts. These effects were accompanied by acute lymphocytopenia and marked depletion of lymphocytes from lymphoid tissue. In contrast to high dose steroids (see above), no evidence of lymphocyte destruction within lymph nodes was observed. In addition, adoptive transfer studies documented that, " . . . for a few generations, the descendants of cells rendered incompetent by antilymphocytic sera (ALS) are themselves incompetent. [and that] ALS may act by bringing about a generalized single 'sterile activation' of lymphoid cells which forestalls or supplants all other immunological commitments" [98]. Monaco et al. [120] described prolongation of canine renal allografts using a horse anti-dog lymphocyte preparation.

In a landmark clinical study, Monaco et al. [120a] were the first to report results of heterologous protein administration in humans. A rabbit antilymphocyte preparation was administered to 5 healthy normal individuals, 4 patients with end-stage renal disease (ESRD),

and one patient with chronic lymphocytic leukemia (CLL). The ALS produce a rapid, transient lymphocytopenia. Moreover, 11 of 12 positive delayed-type hypersensitivity (DTH) skin tests present were completely abrogated or markedly decreased in intensity after three subcutaneous injections administered on alternate days [120a]. One moderate and one markedly positive pre-ALS skin test remained negative at 2 weeks despite restoration of peripheral lymphocyte counts to normal. Skin allograft survivals were also found to be prolonged [120a].

Clinical Impact: Pre-CsA vs. Conventional CsA Eras

The central question at issue in the controversy surrounding the utility of antibody induction in the contemporary era of immunosuppressive therapy is whether or not it exerts a compelling beneficial impact on the risk of acute immunologic injury when compared to so-called non-induction protocols. During the pre-CsA era, a number of clinical investigations confirmed an unequivocally beneficial effect on patient survival, graft survival, and both the rate and timing of acute rejection episodes [15, 125, 126, 132, 153b, 162, 163, 166, 174, 179]. In contrast to the pre-CsA era, however, most centers reported acute rejection rates in the 40 – 50% range in patients receiving CsA-Pred or CsA-Pred-Aza whether or not antibody induction was utilized [42a, 57, 58, 90, 106b, 110]. One of the best illustrations of this experience came from The University of Cincinnati in a retrospective analysis of over 350 patients induced with varying regimens including Minnesota antilymphocyte globulin (n = 95), OKT3 (n = 58), ATGAM (n = 104), Nashville Rabbit Antithymocyte Serum (N/RATS) (n = 37), and cyclosporine only (n = 64) [58]. Antibodies were used for 7 – 10 days and CsA started at a dose of 8 mg/kg/day when the serum creatinine dropped under 4 mg/dL. Trough CsA levels were targeted at 250 – 350 ng/mL (WB TDx). Pred and Aza were also utilized. In the CsA-only induction cohort, therapy was initiated at 3 mg/kg/day intravenously (IV) immediately following surgery and levels targeted at 400 – 500 ng/mL [58]. Acute rejection rates in the CsA-only induction cohort (52%) were not significantly different from those occurring in patients treated with MALG (52%), OKT3 (57%), ATGAM (65%), or N/RATS (43%) [58].

In contrast to the above, there were clinical studies implying an immunologic advantage associated with the use of antibody induction in the conventional CsA era. Some of these were not overly compelling, however, in that they reported acute rejection rates that fell within the normative range of 40 – 50% in association with induction but were considerably higher in concurrent CsA-treated controls not receiving antibody. One such study randomized 215 patients to receive either 14 days of OKT3 or no antilymphocyte antibody along with Pred, Aza, and CsA [131]. CsA was initiated at doses ranging from 6 – 12 mg/kg/day. Three-month acute rejection rates were 51% in the OKT3 cohort vs. 66% in control patients ($p = 0.032$) [131]. The mean time to first acute rejection episode was 46 days in the OKT3 group vs. 6 days in controls [131]. Similarly, Abramowicz et al [1992] reported 3 month acute rejection rates of 52% in 56 cadaveric renal allograft recipients receiving OKT3 induction and CsA initiated on the eleventh postoperative day with trough concentrations targeted at 150 – 250 ng/mL, as measured by radioimmunosorbent assay on whole blood) (WB Sandoz RIA) vs. 69% in a control cohort not receiving antibody (n = 52) [3].

The only advantage consistantly attributable to the use of antibody induction observed in the studies summarized above was mitigating the risk of acute rejection during the period of recovery from harvest/preservation ischemic and reperfusion injury by prolongation of the time to onset of first acute rejection episodes. The relevance of this finding to aggregate graft survival is disputed, however. Thus, with reduction in the incidence and sequelae of early immunologic injury no longer universally acknowledged to be among the benefits afforded by the use of antibody induction, controversy and a lack of consensus regarding the advisability of its use emerged during the conventional CsA era [77, 132a, 140, 160]. This issue has become even more complicated with the recent introduction of newer, more potent xenobiotic agents, e.g. FK506, MMF, CsA-ME, and sirolimus (see below).

Monoclonal Antibodies Directed Against the Interleukin-2 Receptor

The present decade has been marked by the development and clinical evaluation of both murine and humanized monoclonal antibodies directed against the α chain of the Il-2R (alternately referred to in the literature as anti-Il-2R, anti-Tac, and anti-CD25). In contrast to polyclonal preparations and the murine monoclonal OKT3, which impact on virtually all phases of the homograft reaction, including antigen presentation and recognition, anti-Il-2R monoclonals exert their immunomodulatory effects during the G1 phase of the lymphocyte cell cycle by blocking the binding of Il-2 to its cell surface receptor.

Initial clinical experience with anti-Il-2R monoclonal antibodies involved the use of murine preparations. Although aggregate experience with these antibodies did not demonstrate a compelling benefit on clinical outcomes when compared to normative regimens, the most encouraging results were reported in a double blind, randomized, placebo-controlled trial carried out in the Netherlands and published in 1995 [177]. In this study, 27 patients received the murine anti IL-2 R preparation on a daily basis for the first 10 days following renal transplantation. The dosage schedule was 5 mg administered immediately following transplantation and 10 mg/day thereafter. Controls (n = 29) received normal saline placebo. Concomitant immunosuppression in both groups consisted of corticosteroids and CsA. Of note, the mean number of HLA-A, -B, and -DR mismatches, respectively, was < 1 in both groups. During the first 10 days following transplantation, 24% of the placebo-treated patients experienced an acute rejection episode compared to none of the patients treated with the antibody ($p = 0.01$). Treatment vs. control acute rejection rates at 1, 3, and 12 months were 4% vs. 24% ($p = 0.05$), 11% vs. 28% (p = ns), and 15% vs. 32% (p = ns), respectively [177]. Despite this beneficial impact on early acute rejection rates, however, one year graft survivals were comparable in the antibody-treated and placebo cohorts (84% vs. 87%, respectively) [177]. No side effects were reported to have occurred as a consequence of the administration of the antibody nor were immunodeficient complications more prevalent [177].

One of the clinical shortcomings associated with murine monoclonal antibodies is a relatively brief elimination half life ($t_{1/2}$ 24 hours for IgG antibodies) occurring as a consequence of the formation of human anti-mouse antibodies [4, 180, 181]. This consideration, along with first-dose reactions associated with the use of OKT3, provided a rationale for the application of molecular engineering technologies to the production of humanized

monoclonal antilymphocyte antibodies. This venture has resulted in the production and clinical evaluation of anti-Il-2R monoclonal antibodies by 2 pharmaceutical houses. Each chimeric preparation is comprised of murine antigen-binding regions and constant portions in the form of human IgG heavy and light chains [4, 180, 181].

In 1995, the first Phase I-II clinical trial involving the use of a chimeric anti IL-2R monoclonal antibody was reported from the United Kingdom [4]. Twenty-four renal transplant recipients received 6 infusions over a period of 24 days with an escalating dosage protocol (dose range 2.5 – 25 mg). In vivo activity was assessed in terms of the time to reappearance of CD25 on the surface of circulating T cells. The chimeric antibody was not immunogenic, and the average elimination $t_{1/2}$ was 13 days [4]. Additional immunosuppressive therapy consisted of either Pred-CsA or Pred-CsA-Aza. Target CsA levels were 70 – 130 mg/mL in the triple therapy group, and 150 – 250 mg/mL in the dual therapy cohort [4]. Thirty-three percent of the patients developed an acute rejection episode during antibody therapy. The remaining two-thirds of patients remained rejection-free at one year [4]. Lymphoproliferative disorders occurred at 9 months following transplantation in 2 patients, both of whom were receiving the triple drug maintenance regimen. No significant adverse events occurred during the course of 144 separate infusions. Acute rejection rates, although high by contemporary standards, were lower than those who encountered historically at each of the two participating centers [4]. Finally, it was concluded from pharmacokinetic profiling that 30 – 40 mg of the chimeric monoclonal used in this study provided one month of absent CD25 when administered in either interrupted doses over 10 days or as a single dose prior to transplantation [4].

Results of a randomized, double-blind, placebo-controlled trial involving 126 primary cadaveric kidney transplants recipients treated with a humanized anti-Il-2R monoclonal antibody were published in 1998 [181]. Patients received 1 mg/kg of the antibody immediately prior to transplantation and at 2 week intervals thereafter to a total of 5 doses. Additional immunosuppressive therapy consisted of CsA, Pred, and Aza. CsA dosage schedules and pharmacokinetic profiles were not described. An additional 134 patients were randomized to receive placebo in lieu of the humanized antibody. The primary study end point was 6 month acute rejection rates. No adverse events occurred in association with administration of the antibody. Biopsy-proven rejections occurred in 22% of the patients receiving antibody vs. 35% of controls ($p = 0.03$). When presumptive rejection episodes were included in the data analysis, these rates rose to 25% and 39%, respectively ($p = 0.04$) [181]. Again, however, the difference in acute rejection rates did not translate into a significant advantage with regard to one-year graft survivals which were 90% in the placebo group vs. 95% in the patients receiving antibody [181]. Suppression of CD25 staining on circulating lymphocytes was first observed at ten hours following transplantation and persisted for up to 4 months [181]. Nonetheless, the study cohorts were comparable with respect to the incidence of immunodeficient complications. Cytomegalovirus (CMV) viremia occurred in 7% of the placebo group vs. 10% of the antibody-treated cohort, while post-transplant lymphoproliferative disease occurred in one placebo patient and 2 patients receiving antibody induction [181].

The rationale for the use of humanized chimeric anti-Il-2R monoclonal antibodies as induction agents derives from the need for relatively few dosage administrations due to their extended duration of immunosuppres-

sive activity, the potential for reuse uncomplicated by the consequences of immunogenicity, the absence of untoward side effects such as first-dose reactions, and ease of administration via a peripheral venous route. Whether these considerations translate into improved clinical outcomes and cost-effectiveness compared to contemporary benchmarks remains to be determined and, as is the case with any induction regimen, is clearly linked to the maintenance regimens accompanying their use (see below).

Cyclosporine (CsA)

Background

Spearheaded by Jean Borel and Sir Roy Calne, the second major era in the evolution of renal transplantation began during the early 1970s with the monumental discovery and development of CsA [16, 17, 20, 20a]. Several clinical trials subsequently reported that use of CsA-based immunosuppressive regimens improved one year-graft survival by up to 30% compared to conventional regimens utilizing Aza and Pred [75, 147, 165, 170]. CsA-based immunosuppressive regimens were also shown to mitigate the adverse impact of many immunologic risk factors historically associated with reduced one-year graft survivals [35, 73, 86, 147]. These included previous transfusions; HLA-A, -B, and -DR mismatches; and strong vs. weak pretransplant immune responder status [35, 73, 86, 147]. CsA was also demonstrated to obviate the need for "immune conditioning" by donor-specific transfusions, third party transfusions, and splenectomy [73, 86]. Of note, a small number of centers did not find that CsA improved one-year graft survivals vs. those obtained with antibody induction and Pred-Aza [50, 127]. These and other studies did, however, confirm that the lymphocyte-specific mechanism of action of CsA was associated with a significant reduction in the rate of immunodeficient complications vs. conventional treatment with Pred-Aza [50, 61, 127].

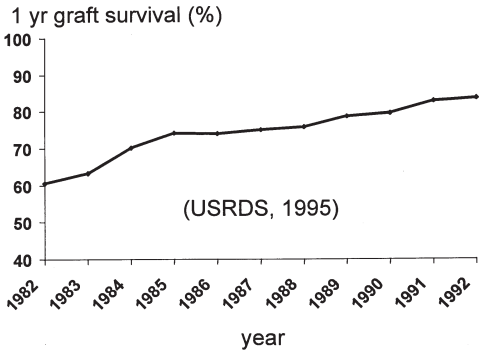

Figure 2. Impact of CsA on 1' CAD One Year Graft Survivals [175].

Reflecting rate of utilization, as well as the obligatory "learning curve" accompanying the first several years of use, the evolution of patient and graft survival during the conventional CsA era is illustrated by the United States Renal Data Systems (USRDS) data displayed in Figure 2 [175]. This improvement in normative clinical outcomes following kidney transplantation occurred despite the fact the procedure was being performed in substantial numbers of high risk patients. Currently, the gold standards established by conventional, CsA-based immunosuppressive regimens encompass one-year patient and graft survivals of ≥ 95% and 85.6%, respectively [193]. The selective effect of CsA on the immune system is also reflected in a change in the leading cause of late patient death from infection and liver failure to complications of cardiovascular disease [32].

Clinical Issues

Despite the revolutionary impact of CsA on the clinical practice of renal transplantation, it has been obvious from the outset of its use that the drug is not a "magic bullet" with an infinitely wide therapeutic index. Two issues in particular have remained of major concern to clinicians and have provided impetus to continued research and development directed at novel immunosuppressive agents representing alternatives or adjuncts to CsA. One of these issues is relatively high normative acute rejection rates (see below). The other derives from concerns about the impact of relationship between long-term CsA use and renal allograft function.

Minimizing Acute Rejection Rates: Importance of Early Drug Exposure

General Considerations

As noted previously, normative acute rejection rates during the conventional CsA era ranged from 40 – 50% regardless of whether an antilymphocyte antibody preparation was used for induction of immunosuppressive therapy. It is important to note, however, that several benchmark outcome studies documented that acute rejection rates well below 20% may be achieved by combining antibody induction with conventional CsA-based maintenance regimens. The premise that early acute rejection rates of 40 – 50% do not represent the best that can be achieved with conventional CsA-based regimens is of obvious relevance to interpretation of the results of clinical trials evaluating the safety and efficacy of newly emerging immunosuppressive agents (see below). As such, it is worthwhile considering what management tactics may have accounted for these discrepant outcomes.

Benchmark Outcome Studies

In contrast to the data summarized above, a number of benchmark outcome studies have been reported during the last several years suggesting that antibody induction, when combined with adequate early CsA drug exposure, may result in an incidence of acute rejection well below the normative rates of 40 – 50%. Kahana et al. [82], for example, reported a 6-month acute rejection rate of 18% in 33 cadaveric renal allograft recipients receiving induction with Aza, Pred, and 5 mg/day OKT3 for 14 days. CsA was initiated on postoperative day 11 with trough levels targeted at 300 – 500 mg/mL (WB Sandoz RIA) [82]. A control group (n = 33) receiving CsA-Aza-Pred and no antibody induction had an acute rejection rate of 52% [82]. Similar results were reported by Grino et al. [1990] who achieved a one-year acute rejection rate of 20% in a cohort of 50 first cadaveric renal allograft receiving induction with equine antilymphocyte globulin (ALG), Pred and IV CsA (2 mg/kg/day) followed by dual Pred-CsA maintenance therapy. Antibody was discontinued only after whole blood polyclonal CsA trough levels reached 400 ng/mL [45]. Patients received dual, CsA-Pred maintenance therapy with CsA trough concentrations maintained in the range of 300 – 600 ng/mL. The one-year acute rejection rate in a concurrent control group of 50 patients who did not receive antibody induction was 40% (p = 0.01) despite the use of a higher post-op dose of IV CsA (5 mg/kg/day) and trough concentrations targeted at 300 – 800 ng/mL [45]. In a subsequent study of 140 primary

cadaveric recipients, the same group compared outcomes associated with use of a polyclonal vs. monoclonal antibody preparation during induction [46]. Both cohorts received initial treatment with IV CsA followed by dual CsA-Pred maintenance therapy with trough concentrations targeted at 150 – 250 ng/mL (WB Sandoz monoclonal RIA) [46]. The combined 3-month acute rejection rate for all study patients was 15.7% with a mean time to first acute rejection episode of 3 ± 2 weeks [46].

In a more recent study reported by Brennan et al. [19], 72 patients were randomized to receive either a rabbit (n = 48) or equine (n = 24) anti-thymocyte globulin preparation along with Pred and CsA-ME (see below). Aza or MMF was added to Pred-CsA in 72% and 25% of patients, respectively [19]. CsA pharmacokinetic profiles were routinely utilized to establish adequacy of absorption and guide individualization of dosage schedules prior to discontinuing the antibody preparation. The acute rejection rates in patients receiving the rabbit antibody was 4.2%, compared to 25% in the equine cohort ($p = 0.01$) [19]. The overall rejection rate in this study was 11% [19]. Rates of freedom from graft loss, patient death, or acute rejection were 94% vs. 61%, respectively ($p < 0.0001$) [19]. Similarly, Cardella et al. [23] reported a 6 month acute rejection rate of 25% in 77 recipients of immunologically "low risk" living related donor allografts treated with rabbit anti-thymocyte serum, Pred, Aza, and the conventional preparation of CsA. CsA was initiated IV and target trough concentrations following conversion to oral therapy were 200 – 300 ng/mL [23]. In contrast, a cohort of similar patients receiving no antibody induction experienced an acute rejection rate of 42% despite setting higher target trough levels (350 – 450 ng/mL) [23]. Another recent study documented a 3-month acute rejection rate of 11% in a group of patients receiving induction with a murine monoclonal anti-Il2R antibody (see below) and maintenance therapy with corticosteroids and CsA [177]. CsA was dosed at 2 mg/kg/day IV for the first 2 post-transplant days with oral doses subsequently adjusted to achieve target trough concentrations of 300 ng/mL for the first 3 months [177]. The acute rejection rate in a control cohort receiving placebo in lieu of antibody was 28% [177]. Finally, a 6-month acute rejection rate of 9.2% was reported from our institution in a series of 59 primary cadaveric renal allograft recipients receiving induction therapy with a polyclonal rabbit antilymphocyte serum which was administered until simple pharmacokinetic profiling documented adequate CsA absorption and dosage schedules were adjusted to achieve trough levels of 350 – 400 ng/mL (WB Tdx) [106]. The majority of patients in this series were on dual drug maintenance therapy with Pred and the conventional preparation of CsA (n = 40) [106]. The newer xenobiotic agents, namely FK506, MMF (MMF), and CsA-ME were utilized on an individualized basis. The combination of FK506 or CsA-ME and Pred was given to 11 and 4 patients, respectively, and 4 individuals received triple drug therapy with Pred, MMF, and CsA-ME [106].

The Pharmacology of Immunologic Risk

One very important consideration in the discrepancy between normative and benchmark acute rejection rates in renal transplant recipoients receiving conventional CsA-based immunosuppressive regimens was elucidated in a landmark clinical study demonstrating that early CsA drug exposure represents a major determinant of immunologic risk [106b]. The subjects of this investigation

were 160 primary renal allograft recipients (99 cadaveric, 61 living related donor) receiving dual Pred-CsA induction and maintenance therapy. Detailed CsA pharmacokinetic profiles were obtained serially in all patients and correlated with clinical outcomes. Consistent with era norms, the overall acute rejection rate in this study population was 51% [106b]. The compelling observation was that CsA bioavailability and rate of elimination, measured at the time of the third orally administered dose of CsA, were highly significant predictors of both acute rejection and one-year graft loss [106b]. With regard to specific pharmacokinetic parameters, rapid oral clearance, reduced area under the concentration-time curve, and lower trough CsA concentrations were each demonstrated to correlate strongly with adverse immunologic outcomes. These data are summarized in Figure 3 [106b]. Aggregate pharmacokinetic profiles of patients with and without acute rejection during the first post-transplant month are shown in Table 1 [106b].

Given the particular importance of establishing adequate immunosuppression during the early post-transplant period as noted by Starzl over 20 years ago [164], the observations reported by Linholm and Kahan [106b] provide strong support for the premise that the discrepancy between benchmark and normative acute rejection rates associated with the use conventionalCsA-based immunosuppressive protocols derive to a substantial extent from what may be characterized as CsA pharmacokinetic vulnerability. More specifically, interindividual variability in CsA absorption and rates of elimination, combined with protocol-specific differences in dosage schedule, time to initiation of therapy, and target trough levels, are likely to result in a broad range of early drug exposure in a given patient population. As such, an indeterminant but clinically important number of patients will be at

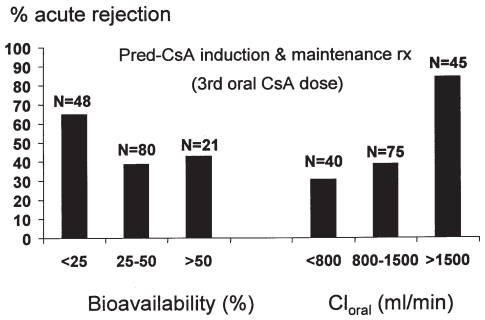

Figure 3. Early CsA Pharmacokinetic Profiles vs. Risk of Acute Rejection [106b].

relatively high risk of acute immunologic injury in the absence of an inordinately strong, intrinsic alloimmune response.

Early CsA pharmacokinetic vulnerability may also account for the frequently reported observation that antibody induction delays the onset but does not reduce the incidence of acute rejection episodes in patients receiving conventional CsA-based immunosuppressive regimens (see above). That is, CsA drug exposure may not become a relevant clinical risk until the protective umbrella afforded by an antilymphocyte antibody is removed, whereas it is a matter of relatively immediate consequence in the absence of antibody induction.

Finally, it is arguable that establishing adequate CsA exposure prior to or concomitant with discontinuation of antibody induction therapy may represent one variable accounting for the lower rates of rejection reported by Kahana et al. [82], Grino et al. [45, 46], van Gelder et al. [177]), Lewis et al. [106], Cardella et al. [23], and Brennan et al. [19] summarized previously. Additional evidence supporting a strong correlation between CsA "drug exposure" following discontinuation of antibody induction and acute rejection risk was presented in retrospective study of 401 cadaveric and 325 living related donor adult renal transplant recipients from the University

Table 1. Cyclosporin Oral Pharmacokinetic Parameters (24-hour dosing interval) in Patients with Acute Rejection During the First Posttransplant Month (n = 60) vs. Patients without Acute Rejection (n = 70), and in Patients for whom 24-hour AUC Studies were Performed 0 – 4 Days before Treatment for Acute Rejection (n = 30) vs. Time-matched AUC Studies in Nonrejecting Patients (n = 70).

	First Oral Study			Average month 1		
	Rejecting patients	Nonrejecting patients		Rejecting patients	Nonrejecting patients	
Parameter	(n = 60)	(n = 70)	p Value*	(n = 60)	(n = 70)	p Value*
Dose (mg/kg/24 hours	11.2 ± 4.7	11.0 ± 3.9	NS	10.7± 4.6	10.5 ± 3.4	NS
C_6 (ng/mL)	705 ± 315	963 ± 471	< 0.002	697 ± 278	974 ± 339	< 0.001
C_{14} (ng/mL)	259 ± 145	377 ± 190	< 0.001	268 ± 124	379 ± 155	< 0.001
C_{24} (ng/mL)	160 ± 82	259 ± 1234	< 0.001	165 ± 79	275 ± 132	< 0.001
t_{max} (hr)	3.6 ± 1.8	4.0 ± 2.0	NS	3.7 ± 1.5	4.0 – 1.6	NS
C_{max} (ng/mL)	1139 ± 459	1475 ± 517	0.001	1140 ± 425	1497 ± 475	< 0.001
Peak-trough (ng/ml)	980 ± 421	1217 ± 484	< 0.02	968 ± 380	1238 ± 431	< 0.001
Peak/trough C_{av} (ng/mL)	8.28 ± 3.70	6.79 ± 3.70	< 0.01	8.16 ± 3.33	6.70 ± 3.03	< 0.005
C_{av} (ng/mL)	420 ± 163	573 ± 197	< 0.001	418 ± 148	592 ± 169	< 0.001
CL_{oral} (mL/min)	1582 ± 903	983 ± 445	< 0.001	1527 ± 888	908 ± 399	< 0.001

Data are mean values ± SD *Mann-Whitney *U* test.
Adapted from [106b] with permission

of Minnesota [72]. All patients in this study were treated with corticosteroids, Aza, and the conventional preparation of CsA. Cadaveric allograft recipients also received a course of equine MALG or other antibody preparation during induction [72]. Multivariate analysis showed that cadaveric donor source, ≥ 1 HLA mismatch, and CsA trough levels < 150 ng/mL measured by high pressure liquid chromatography (HPLC) at 7 days emerged as a significant predictors of both acute and chronic rejection [72]. Acute rejection rates among cadaveric and living related donor recipients whose one week CsA trough concentrations exceeded 150 ng/mL were 14.9% and 22.3%, respectively [72]. In contrast, one-week trough concentrations < 125 ng/mL were associated with acute rejection rates of 42.9% and 45.5% in cadaveric and living related donor recipients, respectively [72].

Summary

Several, benchmark clinical outcome studies have suggested that acute rejection rates < 20% may be obtained by combining antibody induction with conventional CsA-based maintenance regimens. An important element of the protocols achieving these results appears to be attaining adequate CsA exposure by utilization of therapeutic drug monitoring prior to and following discontinuation of antibody therapy. The premise that early acute rejection rates of 40 – 50% do not represent the best that can be achieved with conven-

tional regimens is of obvious relevance to the interpretation of results of clinical trials evaluating the safety and efficacy of combination therapies utilizing newer xenobiotic agents.

Long-Term Use: Clinical Issues

General Considerations

As previously noted, there are 2 rather contradictory concerns over the long-term use of CsA in renal transplant recipients. The first is that insufficient drug exposure due to intermittently reduced bioavailability of the conventional preparation of CsA predisposes to graft loss consequent to chronic rejection [80]. This concept has provided a rationale in support of the controversial tactic of routinely converting renal allograft recipients with stable long-term function from the conventional oil-based to the micro-emulsion preparation of CsA (CsA-ME) [80]. The counterpoint issue derives from concerns that long-term exposure to therapeutic doses of CsA may cause premature renal allograft failure consequent to a progressive, toxic nephropathy [10, 105, 122, 124].

Evolution of Renal Allograft and Native Kidney Function

Apprehension over the potential for long-term use of CsA to cause irreversible loss of renal function originated with the landmark population study of 32 heart transplant recipients reported by Myers et al. in 1984 [122]. Glomerular filtration rate (GFR) and renal blood flow (RBF), determined by measurement of inulin and paraaminohippurate clearances, respectively, were reduced in these patients when compared to an historical control group treated with Pred-Aza [122]. Curtis et al. [28] subsequently established that the same type of acute vasomotor dysfunction described in the native kidneys of the Stanford heart transplant patients was present in CsA-treated renal allografts and was reversed with conversion to Pred-Aza (Table 2). The Stanford heart transplant study also found that aggregate reciprocal creatinine concentrations (1/Cr) declined over the first 6 postoperative months in the CsA-treated patients (Figure 4) [122]. In contrast, aggregate 1/Cr values initially increased over baseline and remained stable thereafter in the historical controls receiving Pred-Aza (Figure 4) [122]. Moreover ESRD occurred in 3 of the patients in the CsA cohort [122]. Concern that CsA use for ≥ 1 year may directly result in the development of ESRD in renal extrarenal solid organ transplant recipients also derived from histologic studies describing interstitial fibrosis, obliterative microangiopathic changes, and hypertrophy, ischemic involution, and sclerosis of glomeruli in the native kidneys of CsA-treated cardiac transplant recipients [123a, 124].

Reported during the mid-1980s, the alarming observations summarized above obligated

Table 2. Hemodynamic Parameters in Renal Transplant Recipients before and after Conversion from CsA to Aza [28]

Parameter	MAP (mm Hg)	RVR (mm Hg/ mL/min)	ERPF (mL/min)
Before	108 + 4	50 + 6	236 + 16
After	98 + 3*	32 + 3**	322 + 21**

*p< .05 vs. CsA; **p< .O1 vs. CsA

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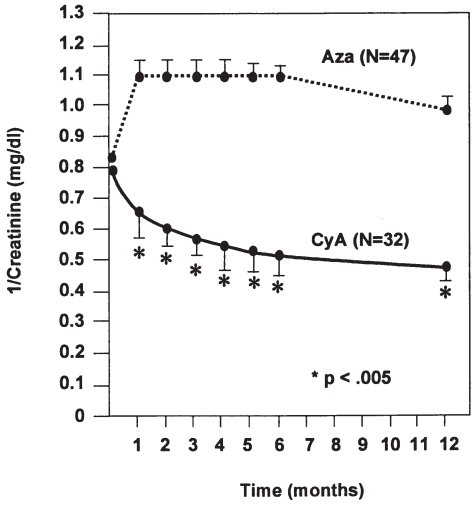

Figure 4. 1/Cr vs. Time in CsA- and Aza-Treated Cardiac Transplant Recipients: The 1984 Stanford Study [122].

clinicians charged with the care of kidney transplant recipients to determine whether the extraordinary clinical benefits associated with use of this revolutionary immunosuppressive agent would be offset by the occurrence of a progressive, toxic nephropathy leading to premature renal allograft failure. To formulate a perspective on this important question, one must begin with consideration of the pathogenesis of the leading cause of long-term renal allograft attrition, namely, chronic rejection [32]. From the standpoint of renal allografts, chronic rejection is defined by a progressive, irreversible loss of function associated with histopathologic changes encompassing interstitial fibrosis, intimal proliferative disease involving the microvasculature, and sclerosis as well as ischemic involution of glomeruli [32a, 37, 93, 109].

Both immunologic and nonimmunologic mechanisms have been implicated in the pathogenesis of the vascular remodeling that results in the ischemic involution of renal allografts and other vascularized organ transplants [32a, 37, 93, 109]. Nonimmunologic vectors of injury that may contribute to the development of chronic rejection include harvest and preservation-related ischemic and reperfusion injuries; exposure to nephrotoxic drugs; and primary as well as systemic disease processes impacting adversely on renal allograft structure and function. Given the multiple vectors of injury linked to the development of chronic rejection, alternative terminologies are emerging that are generally more descriptive and less prone to be interpreted as implying an exclusive role for immunologic injury in its pathogenesis [32a, 37]. These include “graft arteriopathy” and, as characterized by Bennett, “chronic renal allograft failure syndrome” [10, 32a, 37].

It is self-evident that any particular one of the vectors of injury implicated in the pathogenesis of the chronic renal allograft failure syndrome may be more or less predominant in an individual patient. As such, it is difficult to generalize regarding the isolated impact of long-term CsA use on its development in the clinical setting. Nonetheless, a large number of population studies have been undertaken during the last 15 years addressing this critical issue in the settings of renal and extrarenal transplantation as well as the treatment of autoimmune diseases and primary glomerulopathies. The remainder of the present section will review representative examples of these data. Before proceeding, however, it should be noted that FK506 has been demonstrated to cause both acute vasomotor renal dysfunction and long-term renal allograft histopathologic changes similar to those described in CsA-treated patients [143]. As such, issues related to short and long-term use of CsA may be presumed to apply to this “new era” T-cell activation inhibitor as well.

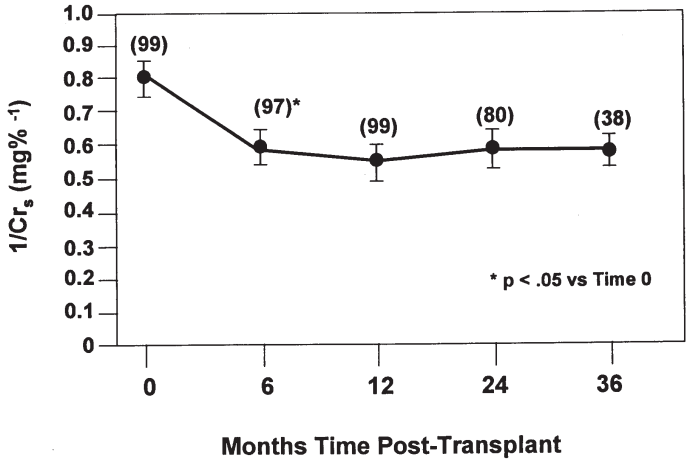

Figure 5. Evolution of Renal Function in CsA-Treated Cardiac Transplant Recipients at the Texas Heart Institute [100].

Long-term Studies of Renal Allograft Function

As noted previously, the original Stanford heart transplant study implicating CsA use for ≥1 year as a cause of deterioration of native renal function did so in large part on the basis of finding that the trajectory of the line formed by plotting aggregate 1/Cr vs. time was sharply down sloping through the first 6 post-operative months (Figure 4) [122]. As such, retrospective population studies examining the evolution of renal allograft function associated with long-term CsA also focused on analyses of serial aggregate serum creatinine concentrations that were extended to follow-up periods of ≥ 5 years [12, 99, 100, 105, 106a]. In fortunate contrast to what one might have predicted from the early heart data, single center reports from Houston and Huddinge demonstrated that aggregate renal allograft function measured from 1 to > 5 years following transplantation did not accelerate with time or decline at a rate exceeding that of historical controls treated with Pred-Aza [12, 99, 100, 106a]. Similar inferences were drawn from a review of 13 studies analyzing outcomes in > 4,000 CsA-treated renal transplant recipients followed for up to 10 years [105].

Extended follow-up of larger numbers of extrarenal transplant recipients has also reconciled the apparent discrepancy between the renal allograft data summarized above and pessimistic expectations extrapolated from the original Stanford heart transplant data. More specifically, population studies evaluating the evolution of aggregate 1/Cr values, as well as iothalamate clearances, in cardiac and hepatic allograft recipients have shown that aggregate native kidney function declines significantly vs. baseline values during the early post-transplant period but remains stable thereafter [43, 44, 100, 124]. One early example of such data, reported from the Texas Heart Institute in 1991, is shown in Figure 5 [100]. The early decline in aggregate native renal function consistently observed in these population studies has been presumed to reflect the effects of the increased renal vascular resistance that occurs uniformly in patients receiving therapeutic doses of CsA or FK506 [28, 43, 44, 100, 101, 122].

Methodologic pitfalls inherent in the retrospective population studies of renal allograft recipients referenced above inspired a number

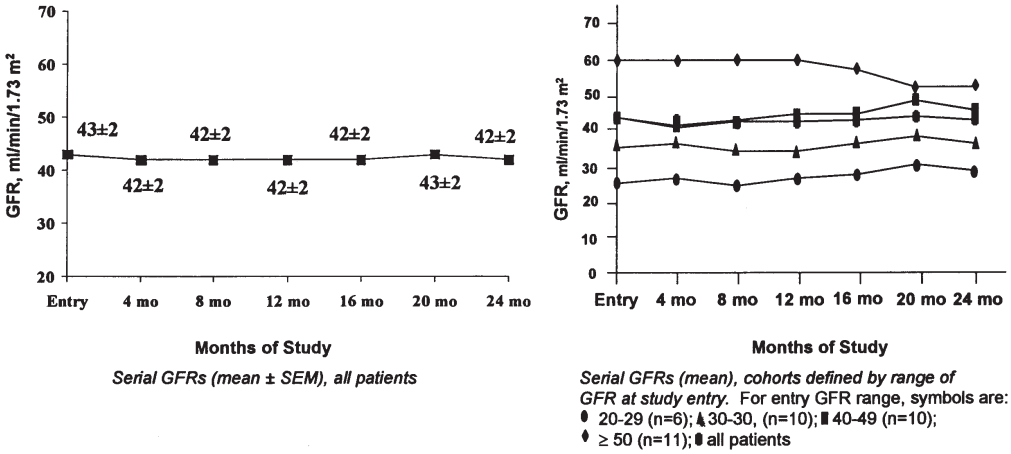

Figure 6. Serial Glomerular Filtration Rates in 37 CsA-Treated Renal Allograft Recipients Followed for Two Years at the University of Texas, Houston [102, 105].

of prospective analyses in which serial measurements GFR were performed prospectively in relatively small cohorts of CsA-treated renal transplant recipients [6, 102, 103, 105, 157]. At the University of Texas Medical School at Houston, GFRs were measured at 4 month intervals for 2 years in a group of 44 CsA-treated patients ranging from 2 months to 9 years following renal transplantation at the time of study entry [102, 103]. Aggregate GFRs did not change significantly in the study population as a whole or within cohorts defined on the basis of GFR at the time of study entry (20 – 29, 30 – 39, 40 – 49, and ≥ 50 mL/min/1.73m^2 (Figure 6) [102, 103, 105]. Of note, stability of function within each of these "entry GFR" cohorts was not attributable to selective reduction of CsA dosage either prior to or during the study period [102, 103, 105]. Similar findings were reported from studies performed at UCLA and the University of Minnesota [6, 157].

Retrospective population studies have also failed to show that the rate of renal allograft failure beyond one year in patients receiving CsA-based immunosuppressive therapy either accelerates with time or exceeds that observed in association with the use of Pred-Aza maintenance therapy. The European Multicentre Trial [12], for example, reported 10-year survivals of 35% vs. 29% in the CsA (n = 117) and conventional Pred-Aza (n = 115), intent-to-treat cohorts, respectively ($p < 0.05$) [12]. Of note, patients randomized to receive CsA in this early study were converted to Aza if an acute increase in serum creatinine concentration occurring in the early post-transplant period did not improve following 2 courses of antirejection therapy [12]. This occurred in 46 patients while 5 individuals in the conventional group were switched to CsA. Patients with graft function at one year were grouped into 3 cohorts defined on the basis of always receiving CsA, always receiving Aza-based therapy, and early conversion from CsA to Aza as described above. Ten-year graft survivals in these cohorts were 56%, 54%, and 39%, respectively [12]. These data were consistant with results of a meta-analysis of studies assessing outcomes associated with the long-term use of CsA that found renal allograft failure rates were consistently compara-

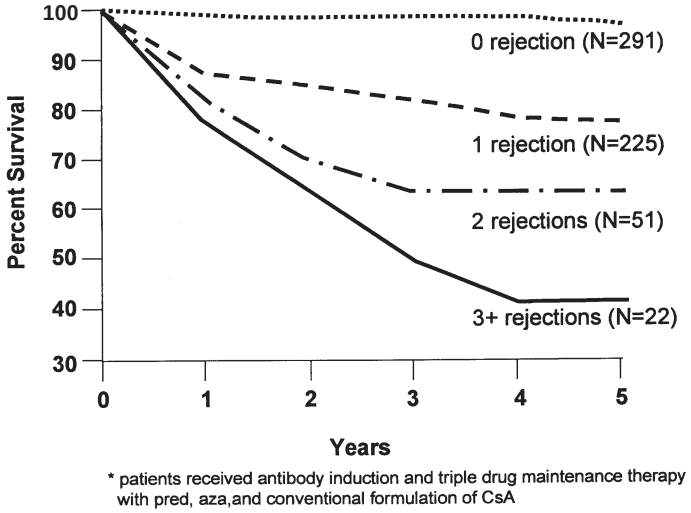

Figure 7. Impact of Acute Rejection Episodes on Immunologic Graft Survival in First CAD Renal Allograft Recipients: University of Wisconsin* [141].

ble to or less than those associated with the use of Pred-Aza maintenance regimens [105].

Another important consideration relating to the notion that long-term CsA use represents a singular risk factor for the development of premature renal allograft failure is that graft half-lives during the conventional CsA era did not exceed those obtained with Aza-Pred regimens despite the fact that one-year survivals were improved by 15 – 30% [10, 40]. Data from population studies published during the present decade, however, have not consistently supported this assertion. Long-term graft survivals clearly superior to Pred-Aza historical norms have been reported from the University of Wisconsin, for example, in a review of the 5 year outcomes of 589 CsA-treated, cadaveric recipients transplanted between 1986 and 1992 (Figures 7 and 8) [141]. A particularly noteworthy result is the low rate of long-term attrition among the substantial number of patients with no history of early acute rejection (Figure 7) [141]. Immunologic causes of graft loss as defined in this study were acute and chronic rejection as well as infection attributed to immunosuppressive therapy. Excluded were grafts lost as a result of death with baseline function, recurrent disease, technical complications, and noncompliance. The important impact of acute rejection and death despite renal function on aggregate, long-term outcomes in conventional CsA-treated renal transplant recipients was also demonstrated by the University of Minnesota [110] in an analysis of 6 year graft survivals among 298 primary cadaveric renal transplant recipients (Figure 8). Similar results have also been reported from Ohio State University [34]. Table 3 summarizes data from another study reported by the University of Minnesota that dramatically affirms the quality of long-term outcomes associated with conventional CsA-based immunosuppressive regimens in the absence of severe immunologic injury [110].

Together, the studies of long-term graft survival and function summarized above implicate acute rejection, harvest/preservation-related ischemic injury, and death with function, rather than a drug-induced nephropathy, as the predominant determinants of the aggregate risk of chronic renal allograft failure in patients receiving long-term conventional CsA-based immunosuppressive therapy. It is quite

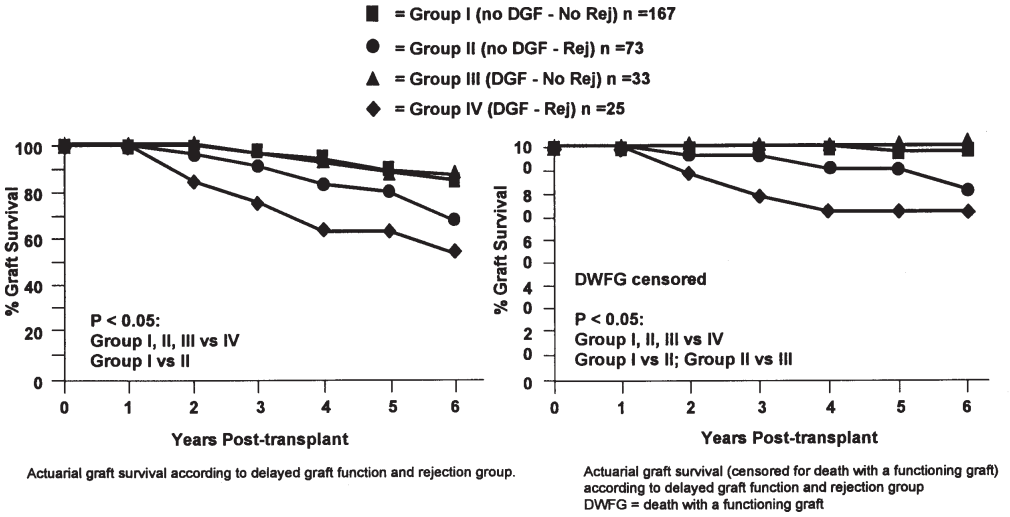

Figure 8. Impact of Early Rejection, Delayed Graft Function, and Death with Function on Long-Term Outcomes in CsA-Treated, First CAD Renal Allograft Recipients at the University of Minnesota [110].

Table 3. Impact of Acute Rejection on the $t_{1/2}$ of Primary Renal Allografts

No. acute rejection episodes		$t_{1/2} \pm$ SE (yr) without death censored	95% confidence interval	With death censored
LivingDonor				
0	(n = 225)	62 ± 23	(16 – 108)	733
1 in 1st yr	(n = 80)	28 ± 13	(3 – 53)[b]	71 ± 50
> 1 early[a]	(n = 44)	6 ± 2	(2 – 9)[b]	7 ± 2
≥ 1 after 1st yr	(n = 26)	4 ± 1	(2 – 7)b	5 ± 2
Cadaver donor				
0	(n = 150)	33 ± 11	(11 – 55)	infinite
1 in 1st yr	(n = 64)	22 ± 10	(3 – 42)	37 ± 22
> 1 early[a]	(n = 50)	5 ± 1	(2 – 7)[b]	6 ± 2
≥ 1 after 1st yr	(n = 14)	2 ± 1	(1 – 4)[b]	3 ± 1

[a]First rejection within 1st year, [b]p < .05 vs. no rejection
University of Minnesota [110]

arguable that these data establish a long-term gold standard for "new era" regimens that will not be easily surpassed.

Long-term Histologic Studies

As noted previously, histologic studies have also provided a basis for concern regarding the impact of CsA on long-term viability of renal allografts. The classical elements of CsA-associated transplant nephropathy were described by Mihatsch et al. [116b] and comprise nodular hyalinosis of the afferent arterioles ("cyclosporine A arteriolopathy [CAA]"), arteriosclerosis, interstitial fibrosis, and glomerular atrophy. Rodent studies found that significant CsA-associated nephropathic changes occurred as a consequence of dosage excess or, in the setting of exposure to therapeutic concentrations of the drug, only in the presence of concomitant renal injury consequent to ischemia, exposure to other nephrotoxic drugs, heminephrectomy, or hypertension [116b, 149, 150]. Genetic predisposition was also found to be a risk factor for the development of nephropathy following exposure to therapeutic doses of CsA [149, 150]. Extending these observations to the clinical setting, Mihatsch et al. [116b] analyzed 12 month biopsy specimens obtained from 90 CsA-treated renal allograft recipients transplanted between 1981 and 1983. Half of these patients received CsA monotherapy at doses achieving trough concentrations (WB, polyclonal RIA) of 1404 ± 1808 ng/ml and 1009 ± 1669 ng/mL at 0 – 30 and 30 – 90 days, respectively [116b]. The following risk factors were found to correlate with development of the structural nephropathy:

– relatively high trough levels during the first 90 days,
– episode(s) of acute CsA nephrotoxicity,
– number of acute rejection episodes,
– concurrent use of nephrotoxic drugs, and
– poor initial function [116b]).

The multifactorial nature of the process resulting in the nephropathy associated with CsA use clearly raises questions regarding the specificity of individual histologic abnormalities. Indeed, Mihatsch et al. [117] caution that ". . . interstitial fibrosis and tubular atrophy without CAA are not pathognomonic for CsA-induced lesions but may be the consequence of any vascular pathology especially vascular rejection". This point is clearly pertinent to the interpretation of histologic data implicating CsA as the proximate cause of the "chronic renal allograft failure syndrome" as well as nephropathic changes in the native kidneys of extrarenal transplant recipients. One early study implicating CsA as a cause of progressive interstitial fibrosis, for example, involved a comparative analysis of biopsies performed at 1 – 4 years following renal transplantation in 28 renal allograft recipients receiving antibody induction and maintained on Pred-CsA vs. an historical control group comprised of 43 patients treated with antibody induction followed by Pred-Aza [89]. CsA dosage schedules were 17.5 mg/kg/day for the first month and 10 mg/kg/day at 4 months in 16 patients ("high dose") and 15 mg/kg/day for 14 days followed by 9 mg/kg/day to 2 months in the remaining 12 ("low dose") [89]. Interstitial fibrosis was found in 9/16 of the "high dose" CsA cohort and 2/12 of the "low dose" patients [89]. CAA was not described in any of the study specimens, and progression of interstitial fibrosis was found in 3/9 CsA-treated patients rebiopsied at 12 – 46 months [89]. Notably, interstitial fibrosis was found in 33/43 biopsies from the Pred-Aza cohort. An additional point of importance in this study was that an undesignated number of grafts in each group were described as having

underlying renal artery stenosis at the time of retrieval and transplantation [89]. Thus, an excessive CsA dosage schedule, underlying predisposition to interstitial fibrosis associated with renal artery occlusive disease in an unidentified number of organs, and a substantial incidence of fibrosis in grafts exposed to long-term Pred-Aza affirm the multifactorial pathogenesis of CsA-associated renal allograft histopathologic changes as suggested by the experimental and clinical observations reported by Ryffel and Mihatsch [116b, 150].

Similar considerations may be applied to a retrospective comparison of biopsies obtained from 59 CsA and 46 non-CsA treated recipients of renal transplants reported by Ruiz et al. [148]. Each cohort was divided into subgroups defined on the basis of biopsies having been performed prior to or following the sixth post transplant month. Mean CsA doses were 11.8 ± 0.8 mg/kg/day from 0 – 6 months and 6.8 ± 0.7 mg/kg/day beyond 6 months. While histologic grading for interstitial fibrosis was comparable in all 4 groups, quantitative morphometric techniques indicated that it was more severe in the CsA vs. Aza cohorts biopsied beyond 6 months [148]. While the authors noted that "appreciating this increase in interstitial fibrosis in comparison to allografts with [pred-aza] immunosuppression is difficult and requires several methods of measurement", they concluded that CsA " . . . is not associated with increased interstitial fibrosis . . . prior to 6 months post-transplant, after which there is a significant increase in fibrosis relative to patients not receiving CsA" [148]. Of additional importance to the interpretation of these data, however, was the fact that 69% of the Pred-Aza cohort biopsied after 6 months were recipients of living donor allografts vs. 46% of the CsA patients. Furthermore, mean creatinine was 0.9 ± 0.4 mgL/dL in the former group vs. 1.5 2.0 ± 0.2 – 0.4 mgL/dL in each of the remaining 3 cohorts [148]. Thus, not only were CsA doses relatively high in this study, but it is arguable that the disproportionate number of living related donor recipients and relative differences in aggregate graft function created a bias favoring the non-CsA over the CsA-treated patients biopsied after 6 months [91, 116b].

Given that afferent arteriolar hyalinopathy is, as defined by Mihatsch et al. [117], the sine qua non of CsA "structural toxicity", additional questions of importance are the incidence of this lesion in the renal transplant population and clinical correlations between its presence and premature graft failure. Addressing this issue in a study of 130 renal allograft nephrectomy specimens obtained between 1 and 5,190 days following transplantation, Mihatsch et al. [117] found 7 cases of severe CAA. Medium-to-severe CAA occurred exclusively in allografts transplanted prior to 1985 and was present in 3/35 specimens obtained beyond one year [117]. Severe CAA was judged to be the proximate cause of allograft failure in 1/130 cases. "Vascular rejection" was determined to be the leading cause of graft failure in this series as well as an historical control cohort of 110 nephrectomy specimens obtained from renal transplant recipients treated with Pred-Aza [117]. These authors also found that the frequency of CAA declined from > 70% during 1981/1982 to < 30% in 1987/1988 and just over 40% during 1989/1990. Of additional note, when present in biopsies obtained after 1985, CAA consistently involved < 10% of arterioles [117]. Finally, CAA was found in 25% of a group of autopsy specimens from patients who expired with a functioning allograft. It was concluded from this body of data that the incidence of CAA was relatively low and that it very rarely represented a proximate cause of renal allograft failure [117].

Histologic Data: Native Kidneys of Cardiac Allograft Recipients

One other body of histologic data invoked as circumstantial evidence implicating long-term CsA use as a major cause of premature renal allograft failure derives from studies of native kidney morphology in extrarenal transplant recipients [10, 124]. One such analysis of heart transplant recipients, published in 1991, warrants particular mention in this regard. In a description of native renal biopsies performed in 10 CsA-treated cardiac allograft recipients at a mean of 37.5 months following transplantation (range 31 – 48 months), Bertani et al. [11] reported global glomerulosclerosis in 9, segmental sclerosis in 8, and ischemic changes in "most glomeruli". Normal, enlarged (24%), and reduced (42%) glomerular tuft volumes were also observed [11]. Finally, all 10 specimens demonstrated juxtaglomerular cell hyperplasia, interstitial fibrosis, and arteriolopathy. On the basis of finding no renal histologic abnormalities in autopsy specimens from 4 patients with end-stage cardiomyopathies matched with the transplant cohort for age, sex, and history of hypertension, CsA was implicated as the proximate cause of the native renal histologic abnormalities observed in cardiac transplant recipients [11].

In contrast to the findings of Bertani et al. [11], however, the University of Texas Medical School at Houston reported that renal histologic abnormalities quite similar to those described in CsA-treated cardiac allograft recipients were consistently observed in an autopsy study of patients with ischemic (n = 6) and nonischemic (n = 10) end-stage cardiomyopathies who did not undergo cardiac transplantation [104]. Interstitial fibrosis, tubular atrophy, and glomerulosclerosis were present in 15/16, arteriosclerosis in 13/16, and arteriolosclerosis in 14/16 [104]. In addition, two of the patients demonstrated nodular, arteriolar hyalinosis resembling CsA arteriolopathy as described by Mihatsch et al. [117]. Similarly, Nizze et al. [129] observed that a "striped form of interstitial fibrosis" occurred to a comparable degree in the native kidneys of heart transplant recipients treated with or without CsA.

Of additional relevance to the study of native renal histopathology in CsA-treated cardiac transplant recipients is that morphologic abnormalities were found in the kidneys of 25/50 patients with congestive heart failure reported by Paul et al. [139] in a classical descriptive autopsy study published in 1957. Findings included arteriolar sclerosis, interstitial fibrosis, and "dilatation of the glomerular space" [139]. The latter observation is of particular interest in view of more recent speculation that this finding, when observed in the kidneys of CsA-treated heart transplant recipients, may reflect compensatory hypertrophy developing in response to the destructive effects of the drug on other glomeruli [10, 124].

Basic experimental observations of the impact of myocardial insufficiency on glomerular hemodynamics provide additional perspective on the interpretation of native kidney histopathology described in CsA-treated heart transplant recipients. Ichikawa et al. [1990] described efferent arteriolar vasoconstriction associated with increased glomerular capillary hydraulic pressure and single nephron filtration fraction in response to myocardial insufficiency produced by coronary occlusion in a rat model [71]. Additional renal hemodynamic abnormalities found in these animals were not dissimilar to some of those attributed to CsA, namely, afferent arteriolar vasoconstriction and declines in glomerular capillary flow, single nephron filtration rate, and glomerular capillary permeability [8, 71, 168. 186]. Thus, CHF may be a proximate

cause of glomerular hyperfiltration and, as such, predispose to sclerotic renal injury.

Rate of End-stage Renal Disease (ESRD) in Heart and Lung Allograft Recipients

Another concern deriving from the heart transplant experience derived from the 1984 Stanford study [122] in which it was reported that 3/32 patients receiving CsA for ≥ 1 year ESRD. While these patients were among the first heart transplant recipients to be treated with CsA, it is clear that the rate of ESRD was, to say the least, alarming. Fortunately, however, as experience has evolved to encompass several hundred such patients with more extensive follow-up times, the reported incidence of ESRD has been considerably lower than what might have been expected by extrapolating from the early Stanford data. Four large centers representing 1,090 patients followed for periods of 3 – 14 years, for example, reported ESRD rates of 1.0 – 3.3%, although another single center has reported a rate of 6.5% in 293 patients followed from 3 – 9 years [41, 44, 100].

The clinical and experimental observations summarized above suggest that restraint is merited in implicating long-term CsA use as a singular cause of the structural abnormalities observed in the native kidneys of cardiac transplant recipients, particularly in the absence of baseline, pre-transplant histology. Consistent with the clinicopathologic correlations reported by Mihatsch et al. [116b] in CsA-treated renal allograft recipients, it is arguable that the variability in reported rates of ESRD following cardiac transplantation reflects the importance of extenuating clinical circumstances impacting independently on renal reserve and morphology [100].

Similar considerations apply to the realm of lung and heart-lung transplantation. Zaltzman et al. [191] analyzed renal function in a group of 30 CsA-treated lung allograft recipients transplanted between 1983 and 1992 and followed for a mean of 39 months (range 6 – 60 months). Mean creatinines increased from 0.85 ± 0.04 mg/dL M to 2.06 ± 0.16 mg/dL (75 ± 3.5 μM to 182 ± 14 μM), and 2 patients developed ESRD. Pattison et al. [138] evaluated serial creatinines in 67 heart-lung recipients who were transplanted between 1981 and 1992 and followed for a mean of 50 months (range 6 – 140 months). Aggregate serum creatinine concentration increased from a baseline level of 0.96 ± 0.03 mg/dL to 1.6 ± 0.1 mg/dL at 6 months and 1.9 ± 0.1 mg/dL at the end of follow-up [138]. Three patients developed ESRD. Consistent with the results of retrospective studies of the evolution of renal function in CsA-treated recipients of extrarenal transplants reviewed previously (see above), the greater part of the observed increases in creatinine concentrations in both of these study populations occurred during the early post-transplant period [44, 100, 138, 191]. More recently, Garrity et al. [39] have followed 204 patients receiving CsA- or FK506-based immunosuppressive therapy for lung transplants performed between 1990 and 1996. ESRD has occurred in only 2 of these patients over a mean follow-up period of 2.9 ± 1.5 years (range 1 – 7 years). In addition, of 124 patients with ≥ 12 month survivals, serum creatinine concentrations were 2 – 3 mg/dL in 32 (26%) and > 3mg/dL in 7 (16%). Of the 39 patients whose creatinines exceeded 2 mg/dL, 20 (51%) were over the age of 60 years at the time of transplantation and 8 (21%) had cystic fibrosis and, as such, an antecedent history of substantial exposure to aminoglycosides [39].

Studies of Native Kidney in Patients with Autoimmune Disease

Autoimmune diseases comprise yet another clinical setting in which abnormalities of native renal structure and function associated with long-term CsA use have been suggested to carry dire implications for renal allografts. In 1986, Palestine et al. [137] published a landmark study of native kidney biopsies obtained from 17 patients with autoimmune uveitis who received CsA for an average period of 2 years. The difficulty inherent in treating this disease was reflected in 2 year daily dosage schedules of ≥ 10 mg/kg in 8 patients, 6 – 9 mg/kg in another eight patients, and < 6 mg/kg in a single individual [137]. Histopathologic findings included interstitial fibrosis (17/17), interstitial infiltration (14/17), "generally unremarkable" glomeruli, and thickening of small arteries and arterioles (15/17) due to intimal swelling and proliferation as well as arteriolar hyaline deposition [137]. CsA was implicated as the primary cause of these structural abnormalities on the basis of their general absence in a "control group" consisting of 20 non-uveitis patients biopsied for the evaluation of microscopic hematuria [137].

In contrast to the uveitis data were observations reported by Landewe et al. [96] in a study of patients receiving CsA for the treatment of rheumatoid arthritis. Renal biopsies were obtained from 11 patients receiving CsA at a mean dose of 3.3 mg/kg/day for 26 ± 5 months (range 15 – 30 months). Tubular atrophy was present in 10, interstitial fibrosis in 5, and mild arteriolopathy in 3 [96]. Seven percent of glomeruli were obsolescent [96]. Of importance, 7 of the patients had been treated with gold or penicillamine prior to receiving CsA. Controls consisted of an autopsy series of 22 rheumatoid arthritis patients who demonstrated renal histologic changes that did not differ in type or severity from the study patients. The authors concluded that "low dose [CsA] does not result in more structural nephropathy than the disease itself" [96]. The importance of both antecedent, nephrotoxic drug exposure and baseline renal function was also emphasized by Nizze et al. [129] in studies of heart and bone marrow transplant recipients. Similary, Feutren and Mihatsch [33]. also found that larger initial CsA doses, older age, and peak increase in creatinine were associated with the occurrence of interstitial fibrosis and/or arteriolopathy in 41/152 biopsies obtained from patients receiving CsA for the treatment of insulin-dependent (Type I) diabetes mellitus and other autoimmune diseases.

Studies involving patients with primary glomerulopathies also point to the presence and severity of underlying renal disease as a fundamental determinant of the occurrence and progression of histologic abnormalities associated with so-called CsA nephropathy. Meyrier et al. [116], for example, studied 22 patients with minimal change disease (MCD) and 14 with focal segmental glomerulosclerosis (FSGS) who received a mean CsA dose of 5.5 ± 0.8 mg/kd/day for an average of 120 ± 15 months (range 6 – 78 months). While "vascular CsA toxicity" was found in 1/22 MCD and 3/14 FSGS patients, the majority of individuals with an initial diagnosis of MCD who did not progress to FSGS had baseline biopsies with no interstitial abnormalities and only "minor" interstitial fibrosis on rebiopsy [116]. Habib and Niaudet [49] presented a retrospective analysis of serial biopsies and GFRs in 42 children receiving CsA for the treatment of MCD (n = 37) and FSGS (n = 5). CsA dose was 6 mg/kg/day and duration of therapy 12 ± 4 months (range 4 – 28 months). The interstitium was normal on 41/42 pretreatment biopsies and showed striped fibrosis in the remaining case. In contrast, first post-

treatment biopsies (4 – 28 months) demonstrated striped fibrosis in 10 patients and extensive, confluent fibrosis in 3 [49]. Repeat biopsies performed at a mean of 38 ± 12 months (range 20 – 63 months) showed progression from normal to striped or confluent fibrosis in 7/20 and 4/20 patients, respectively [49]. No CsA arteriolopathy was found on any biopsy, however, and GFRs remained stable throughout the study period. The authors concluded that "the interpretation of tubular and interstitial lesions in patients with idiopathic nephrosis is hazardous since one cannot exclude with certainty that the changes observed are not related to the possible progression of the disease itself, particularly if lesions of FGS are present" [49]. Finally, a 12-month course of CsA has been associated with a salutary effect on proteinuria and the rate of decline of renal function over a 2-year period in a placebo-controlled study of progressive membranous nephropathy [25]. Similarly, a 5-year period of treatment with 3 – 5 mg/kg/day was reported to have a beneficial impact on proteinuria was also reported in a cohort of 10 adults with idiopathic nephrosis treated with 3 – 5 mg/kg/day over a period of 5 years [29].

Summary and Conclusions

The balance of clinical population studies and experimental data addressing the long-term impact of CsA on renal allograft structure and function continues to support the view that the drug may be used in contemporary dosage schedules for at least 10 years without jeopardizing clinical outcomes. Indeed, recent experience indicates that conventional, CsA-based maintenance regimens have established a standard for long-term outcomes (particularly in the absence of early acute rejection episodes) that will be difficult to surpass. Nonetheless, exposure to relatively high or even therapeutic doses may accelerate the rate of deterioration of renal allografts predisposed to premature morphologic and functional deterioration as a consequence of antecedent or concurrent exposure to other vectors of acute and chronic renal injury, e.g. harvest/preservation-related ischemia, immunologic injury, recurrent or de novo glomerulopathies, systemic diseases, and other agents with nephrotoxic effects. To date, no better approach has emerged for making adjustments when these difficult circumstances come to bear on an individual patient than the empiric exercise of sound clinical judgement.

Micro-emulsion Formulation of CsA (CsA-ME)

Introduction

In an excellent review, Ritschel [146] characterizes micro-emulsions as ". . . heterogeneous, fine-dispersion systems (droplet size < 0.15 μm) composed of 2 immiscible liquids (oil and water), a surface-active emulsifier (surfactant or surfactant mixture), and a co-surfactant. . . . [the CsA micro-emulsion] is composed of propylene glycol (hydrophilic solvent) and corn oil monoglycerides, diglycerides, and triglycerides (lipophilic solvent), using a surfactant (polyoxyl-40 hydrogenated castor oil) and an antioxidant (DL-tocopherol)". Surfactant prevents spontaneous separation of the oil and water moeities, each of which contains a portion of drug in the form of a passenger peptide molecule, e.g. CsA. With regard to the physical properties of the drug-vehicle combination, Ritschel [146] explains that " [when] Micro-emulsions come

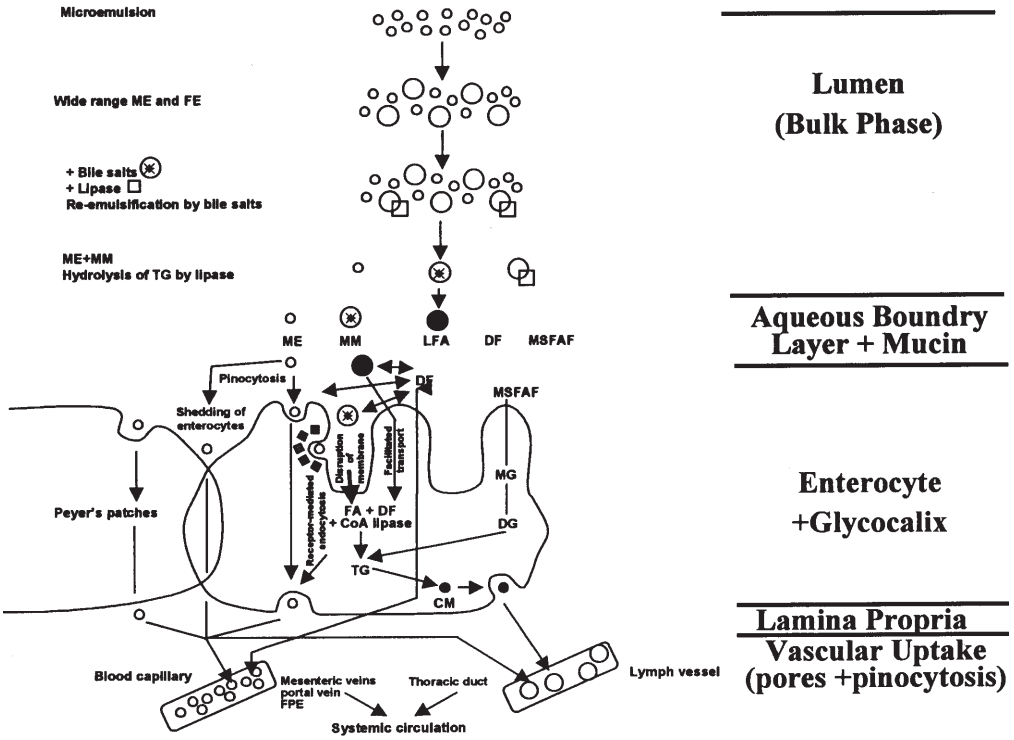

Figure 9. Absorption of Peptides Delivered in a Microemulsion Vehicle [146].

into contact with lipids or water, simultaneous emulsification . . . [generates] particle sizes . . . smaller than the wavelength of light . . . resulting in the formation of a transparent dispersion having low viscosity".

Following oral ingestion of a micro-emulsion preparation in humans, a process of aggregation and modification mediated by bile salts and intestinal lipases produces a mixture of free drug and drug-bearing particles that the micro-emulsion, long-, medium-, and short-chain fatty acids, and mixed micelles convey to and through the intestinal epithelium as illustrated in Figure 9 [146]. The systemic circulation is then accessed via the mesenteric veins, portal system, and lymphatics [146].

Delivery in a micro-emulsion vehicle provides a pharmacologic means for improving the overall of efficiency of intestinal absorption of CsA, eliminating its dependence on bile salts, and, as such, reducing the marked intra- and interpatient variation in bioavailability characteristic of the conventional formulation. Pharmacokinetic studies of stable renal transplant recipients converted from the conventional formulation to CsA-ME have shown a mean increase in aggregate area under the curve of 30% (range 5% to ≥ 60%), shortening of the time to maximum blood concentration from 2 – 6 to 1 – 2 hours, and trough levels that were reduced, comparable to, or exceeded those achieved with use of the conventional preparation [85, 146, 156].

Clinical Impact: Acute Rejection Rates

Given the importance of CsA bioavailability as a determinant of immunologic risk (see above), the potential for de novo use of a micro-emulsion delivery vehicle to improve acute rejection rates vs. norms associated with the conventional formulation is self-evident. To date, however, relatively little data is available addressing the correlation between pharmacokinetic profiles associated with de novo use of CsA-ME and clinical outcomes. Randomized, concurrently controlled, multicenter studies performed in the US and UK have reported acute rejection rates ranging from 27 – 41% and 30 – 55% in renal transplant recipients receiving CsA-ME vs. the conventional formulation, respectively [2, 107, 128]. It should be noted however, that interpretation of the data generated by these studies is somewhat complicated by methodologic pitfalls in the form of disparate induction and maintenance immunosuppressive protocols within study cohorts as well as variable definitions of acute rejection (e.g. treated vs. biopsy-proven vs. "responsive to therapy") [2, 107, 128].

The central question related to the safety of de novo use of CsA-ME is whether or not the attendant increase in aggregate drug exposure over conventional norms will impact on the risks of immunodeficient complications and/or nonimmune toxicities. Comparative clinical studies have indicated that use of CsA-ME does not result in an aggregate narrowing of the therapeutic index [7]. The expectation remains, however, that uniform, de novo use will effect greater aggregate drug exposure compared to the conventional preparation. It follows that pharmacokinetic monitoring in general, and accumulation of data correlating pharmacokinetic parameters with clinical outcomes in particular, are keys to minimizing the likelihood that uniform de novo use of CsA-ME will increase the incidence of adverse events.

Clinical Impact: Chronic Graft Arteriopathy

Another question arising from the availability of CsA-ME is whether improved and less variable bioavailability carries a potential for reducing long-term graft attrition caused by late acute or chronic rejection. One basis for this consideration derives from population studies implicating relatively low aggregate maintenance doses of CsA (< 3.0 – 3.5 mg/kg/day) with an increased risk of both late acute and chronic rejection [60, 189]. As noted previously, intermittent subtherapeutic long-term drug exposure due to intrapatient variability of CsA absorption has also been implicated as a risk factor for chronic rejection. Addressing the latter issue, Kahan et al. [80] analyzed 3,885 CsA pharmacokinetic profiles performed in 204 CsA-Pred-treated renal transplant recipients over a follow-up period of 28 ± 17 months (range 12 – 60 months). The mean coefficient of variation of the average CsA concentration corrected for dose was significantly greater among the 57 patients who developed chronic rejection than those who did not (35.2 ± 12.0% vs. 29.6 ± 9.5%, [$p < 0.001$]) [80]. In contrast, a European study reported values of 18.7% and 28.8% in patients receiving the micro-emulsion (n = 45) vs. conventional (n = 12) preparations, respectively [183].

The concept of a direct relationship between intraindividual variability in CsA absorption and the risk of graft loss from chronic rejection represents a clear rationale for the routine conversion of renal transplant recipients with stable long-term function from the conventional preparation of CsA to the CsA-

ME formulation. This hypothesis is not inconsistant with the observation that the most marked increases in area under the curve attending conversion of patients receiving the conventional preparation of CsA to CsA-ME is likely to occur in individuals with relatively poor absorption of the former [85]. Nonetheless, a degree of ambiguity continues to characterize the clinical data and, as such, a consensus favoring routine conversion of stable patients has not been established to date.

Summary

The availability of a micro-emulsion vehicle has mitigated one of the most difficult problems associated with use of the conventional preparation of CsA , namely, wide inter- and intrapatient variability in absorption. Nonetheless, reliable correlations between basic pharmacokinetic parameters associated with de novo use of CsA-ME and favorable, as well as adverse, clinical events remain to be generated. More extended study will also be of help in addressing the usefulness of routine conversion of stable patients taking the conventional preparation of CsA to CsA-ME VIZ reducing long-term graft attrition consequent to chronic rejection. In the interim, it remains for clinicians to judge the practical issues arising from the unique properties of this pharmacologic vehicle for improving the bioavailability of CsA insofar as they may relate to the well-being of individual patients.

New Xenobiotic Agents

Mycophenolate Mofetil (MMF) and Tacrolimus (FK506)

Clinical Trials: Protocols and Outcomes

There have been 3 multicenter, prospective, randomized, controlled trials evaluating the safety and efficacy of regimens involving de novo use of MMF in combination with CsA and Pred (with and without Aza) [159, 194, 195]. The American MMF trial (MMF-US) assessed 6 month outcomes in first cadaveric kidney recipients receiving 5 – 14 days of antibody induction, CsA, Pred, and either 1 – 2 mg/kg/day Aza (n = 166), 2 g/day of MMF (n = 167), or 3 g/day of MMF (n = 166) [159]. Neither antibody induction nor Aza were included in the protocol of the European trial (MMF-EUR) in which six month outcomes were compared in patients receiving Pred-CsA-placebo (n = 166), Pred-CsA-MMF (2g/day) (n = 167), or Pred-CsA-MMF (3 g/day) (n = 160) [194]. The third, tricontinental MMF study involved centers from Canada, Australia, and Europe (MMF-TRI) [195]. Treatment regimens consisted of Pred-CsA-Aza (n = 166), Pred-CsA-MMF (2 g/d) (n = 173), and Pred-CsA-MMF (3 g/d) (n = 164). Antibody induction was not utilized. Both the MMF-EUR and MMF-TRI studies included relatively small numbers of cadaveric kidney retransplants in addition to primary transplant recipients [194, 195]. A meta-analysis encompassing one year data from all 3 MMF trials was reported by Halloran in 1997 [54].

Two prospective, randomized, controlled, multicenter trials, performed in the US and Europe have evaluated de novo therapy with FK506 vs. the conventional formulation of

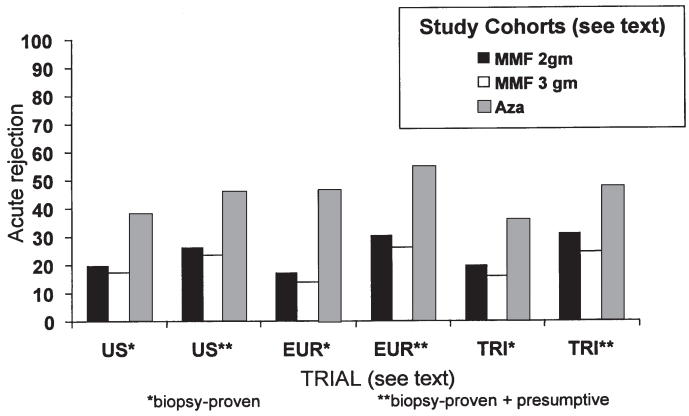

Figure 10. MMF Clinical Trials: Acute Rejection Rates [159, 194, 195].

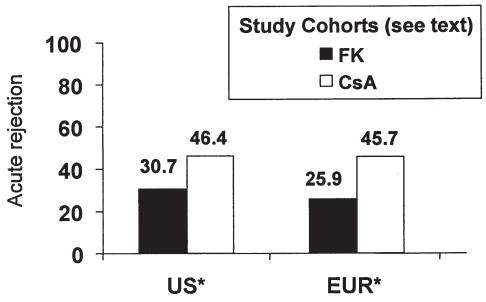

Figure 11. FK Clinical Trials: Acute Rejection Rates [111, 142].

CsA [111, 142]. The US study (FK-US) involved primary cadaveric kidney recipients who received antibody induction and CsA-Aza-Pred (n = 207) or FK506-Aza-Pred (n = 205) [142]. The EUR trial (FK-EUR) involved 303 patients receiving FK506-Aza-Pred and 145 treated with CsA-Aza-Pred and did not utilize antibody induction and [111]. Of additional note, the FK-EUR trial protocol involved reduction of Pred to 5 mg/day at day 43 and discontinuation of Aza after 3 months "where possible" [111].

With normative, 1 year cadaveric graft survivals associated with the use of conventional, CsA-era regimens currently at 85%, it has become a methodologic impracticality to design clinical trials involving new agents to a degree capable of genuinely demonstrating the superiority of one regimen over another in terms of this fundamental end-point [70, 75, 193]. Indeed, 1-year graft survivals achieved in both the treatment and control arms of the MMF and FK506 trials were comparable to the best results reported from the conventional CsA era [27, 54, 70, 111, 136, 142, 159, 194, 195]. Similary, one-year patient survivals ranged from 96 – 99% in all study cohorts with the exception of the 3 g MMF cohort from the U.S. trial (91%) and FK506-treated patients participating in the European trial (93%) [54, 111, 142, 159, 194, 195].

In contrast to the low rates of graft and patient loss noted above, normative rates of acute rejection associated with conventional, CsA-based regimens ranged, as previously noted, from 35 – 50% [47a, 58, 90, 106b, 110]. As such, the primary clinical end-point selected for assessment of efficacy in contemporary clinical trials was the frequency of acute rejection episodes. Indeed, the major beneficial finding reported in the MMF and FK506 trials was that the substitution of MMF for Aza or FK for CsA consistently resulted in significantly fewer patients receiving treatment for acute rejection when compared to conventionally treated controls (24 – 31% vs. 46 – 55%, respectively) (Figures 10 and 11)

[54, 111, 142, 159, 194, 195]. Of note, the trial protocols categorized acute rejection episodes on the basis of the presence or absence of biopsy confirmation [54, 111, 142, 159, 194, 195]. While some patients undoubtedly had full courses of antirejection therapy without undergoing biopsy, an undetermined number of others categorized as having an acute rejection episode received as little as one dose of antirejection therapy. As such, the actual incidence of acute rejection episodes presumably lies somewhere between the biopsy-proven and overall incidence figures. One point to be made with regard to immunologic efficacy is that the frequency of steroid-resistant rejections requiring treatment with antilymphocyte antibody preparations was also consistently higher in conventionally treated controls compared to patients receiving MMF or FK [54, 111, 142, 159, 194, 195].

Clinical Trials: Adverse Events

General Considerations

Adverse events were assessed primarily in terms of cohort-specific rates of occurrence with relatively limited focus on detailing clinical severity. Borrowing terminology from Halloran [53], the present discussion will categorize adverse events as immunodeficient complications or nonimmune toxicities. The former include post-transplant lymphoproliferative disorders (PTLD), cytomegalovirus (CMV) disease, other opportunistic infections, and moderately severe-to-lethal bacterial infections. Nonimmune toxicities encompassed metabolic abnormalities, suppression of hematopoiesis, conditions associated with hypercoagulability, and disorders referable to the myocardium, central nervous system (CNS), and gastrointestinal (GI) tract.

Immunodeficient Complications

With cohort-specific rates of PTLD ranging from 0 – 1.2% in all 5 trials, statistical analyses indicated that increasing net immunosuppression by replacing Aza with MMF, adding MMF to dual CsA-Pred maintenance regimens, or substituting FK for CsA was not associated with a significantly increased risk of this devastating complication vs. that associated with conventional CsA-era norms [54, 111, 142, 159, 194, 195]. While the significance of this finding is self-evident, it is important to note that the studies were, presumably not of a sufficiently high statistical power to permit assessment of the relative rates of PTLD among patients at highest risk, namely, individuals who are Epstein-Barr virus (EBV)-seronegative recipients of kidneys from EBV-seropositive donors and those receiving 2 courses of antilymphocyte antibody therapy.

The overall incidence of opportunistic and other infectious diseases was comparable in patients receiving MMF or FK506 vs. concurrent controls treated with conventional CsA-era regimens [54, 111, 142, 159, 194, 195]. Cohort-specific CMV infection rates, for example, ranged from 11 – 20% [54, 111, 142, 159, 194, 195]. Of note, however, CMV disease was defined in all 5 studies by detection of viremia, the occurrence of a clinical “syndrome”, results of gastric biopsies, and/or nonspecified “tissue invasive disease” [54, 111, 142, 159, 194, 195]. As such, the analyses did not provide a clear depiction of the relative frequencies of asymptomatic, mild, moderate, and severe clinical disease caused by CMV infection. In addition, the frequency with which preemptive ganciclovir was used to mitigate the severity of CMV disease was not reported.

The trials also did not provide comprehensive accounts of the relative clinical severity

of opportunistic infections other than those caused by CMV. The MMF-US, MMF-TRI, and FK-US trials all reported that "opportunistic infection" occurred at seemingly high but equivalent rates, ranging from 44 – 49% in the MMF-US and MMF-TRI trials [142, 159, 195]. In contrast, the FK-EUR study reported that deep/invasive fungal infections (5/303) and Pneumocystic carinii pneumonia (PCP) (6/303) occurred exclusively in FK506-treated patients, but the numbers were too small to establish statistical significance [111]. Of note, however, PCP was not restricted to patients receiving MMF- or FK506-based therapy in any of the other clinical trials [159, 194, 195, 142]. The trial data also did not permit evaluation of the contributions of preemptive ganciclovir, prophylactic acyclovir, or trimethoprim-sulfamethoxazole (TMP-SMX) on the relative rates of PCP or the severity of viral infections.

One parameter that did address the severity of infectious complications reported in the trials was death attributed to sepsis. Combining the data from all 3 MMF studies, septic deaths occurred in 2%, 1%, 0.6%, and 1.8% of patients receiving Pred-CsA-MMF (3g/day), Pred-CsA-MMF (2g/day), Pred-CsA-Aza, and, from the EUR trial, Pred-CsA-placebo, respectively [159, 194, 195]. In the FK-EUR study, combined one year mortality consequent to infection was 3% in patients receiving FK506 ("multiple organ failure/sepsis" in 5 patients and pneumonia in another 4) vs. 1.4% in the CsA cohort (2 cases of pneumonia) [111]. The FK-US trial reported 1-year infectious mortality rates of 2.4% and 1.9% in the FK506 and CsA groups, respectively [142].

Nonimmune Toxicities

Nonimmune toxicities encountered most often in the MMF trials were gastrointestinal (GI) and hematologic [159, 194, 195]. With regard to the former, the frequencies of diarrhea, nausea, and vomiting were comparable in treatment vs. control cohorts. Again, however, the data did not permit comprehensive assessment of the relative clinical severity of these symptoms. While severe GI complications were relatively infrequent, they were noted to occur more often in MMF-treated patients, particularly those receiving 3 g/day [159, 194, 195]. GI bleeding, for example, did not occur in the placebo group of the MMF-EUR trial but developed in 1.2% of patients receiving MMF/2g/day and 2.5% of those treated with 3g/day [194]. Similarly, the MMF-US trial documented GI bleeding in 1.2% of patients receiving Aza vs. 4.2% in each of the MMF cohorts [159]. Rates of "gastroenteritis" in the MMF-EUR study were 1.2% in placebo-treated patients, 2.4% in those receiving MMF/2g/day, and 4.4% in the MMF/3g/day cohort [194]. In contrast, the MMF-US trial reported that gastritis and/or enteritis occurred in 1.2%, 11.6%, and 10.2% of patients receiving Aza, MMF/2g/day, and MMF/3g/day, respectively [159].

With regard to hematologic complications, the MMF-TRI trial reported that leukopenia requiring dose reduction or drug withdrawal occurred in 24%, 15%, and 29% of the cohorts treated with Aza, MMF/2g/day, and MMF/3g/day, respectively [195]. In the MMF-EUR trial, leukopenia developed in 4.2% of placebo-treated patients vs. 10.9% in the MMF/2g/day group and 13.8% in patients treated with MMF/3g/day [194]. In contrast, the MMF-US trial found that leukopenia occurred at equivalent rates in patients receiving Aza, MMF/2g/day, and MMF/3g/day and led to drug withdrawal in "0 – 2.4%" of patients in each cohort [159]. The MMF-US study also reported that the most frequently encountered hematologic abnormality was anemia that,

Table 4. FK506 Trials: Adverse Events with Significantly Different Rates of Occurrence between Study Cohorts [111, 142]

Cohort	European Trials (% of pts)			US Trials (% of pts)		
	FK506	CsA	p value	FK506	CsA	p value
↑ creatinine	35	21	0.03	45	42	0.434
hyperglycemia"	16	7	0.01	20	4	0.001
diabetes	12	2	0.001	20	4	0.001
cholesterol	–	–	–	8	14	0.031
tremor	35	12	0.001	54	34	0.001
paresthesia	–	–	–	23	16	0.041
diarrhea	22	10	0.005	44	41	0.495
angina	11	3	0.018	19	13	0.072
arrythmia	1	6	0.01	–	–	–
DVT*	–	–	–	5	0.5	0.003
acne	3	10	0.003	–	–	–
gingiva**	1	6	0.01	0.5	9	0.011
alopecia	–	–	–	11	1	0.001
pruritis	–	–	–	15	7	0.011

*deep veinous thrombosis, **gingival hyperplasia

like leukopenia, occurred at equivalent rates in all study groups (range 36 – 39%) [159].

A combined summary of nonimmune toxicities found to occur at significantly different rates in FK506- and CSA-treated patients by the US and/or European trials is shown in Table 4 [111, 142]. The relatively high incidence of post-transplant diabetes mellitus (PTDM) associated with the use of FK506 is of obvious concern, although the trials did not control for the well-known risk factors of age > 45 years, obesity, and a family history of diabetes. From a demographic standpoint, the US trial found that patients of African or Hispanic descent were 3.3 times more likely to develop FK506-associated PTDM than caucasians [142]. Both trials noted a relationship between PTDM and FK506 drug exposure, as reflected by dose or trough levels, and reported that PTDM was reversible in some patients [111, 142].

Cohort-specific frequencies of GI complications reported in the FK-US and FK-EUR trials ranged from 8 – 44% but were comparable in FK506- and CsA-treated patients [111, 142]. Again, however, the data analysis did not address relative severity of GI symptoms [111, 142]. The administration of calcineurin inhibitors to patients at high risk of deep venous thrombosis (DVT) presents a clinical concern that the trial results suggest may prove to be more compelling in the case of FK506 (Table 4). Data from the FK506 trials addressing cardiac abnormalities were inconclusive. The European study found higher rates of angina in the FK506 cohort (10.6% vs. 3.4%, p = 0.02) and more frequent dysrhythmias in patients receiving CsA (2.3% vs. 6.2%, p = 0.01) [111].

Study Withdrawal

Each of the trials addressed the aggregate severity of immunodeficient complications and nonimmune toxicities in terms of the frequency of study withdrawal. Of note, a rather marked difference in premature withdrawal rates between FK506 and CsA cohorts was reported in the FK-EUR trial (16.5% vs. 2.8%, respectively) [111]. Specific reasons for withdrawal from FK506 in this study were as follows: neurologic and/or cardiologic problems (4.6%), "renal disorders" (3.6%), CMV infection (2%), PCP (1.3%), PTDM (1.3%), PTLD (1%), anemia (0.7%), and "hepatic disorder" (0.3%) [111]. CsA was withdrawn from 1.4% of patients for "renal disorders" and 1.4% for "malignancy" [111].

The MMF-EUR trial reported premature withdrawal due to adverse events in 14%, 18%, and 26% of the placebo, MMF/2g/day, and MMF/3g/day study groups, respectively [194]. In contrast, the Aza, MMF/2g/day, and MMF/3g/day cohorts from the MMF-TRI study withdrew at comparable rates (14%, 13%, and 18%, respectively) [195]. An "unsatisfactory therapeutic response" was noted to be the leading reason for withdrawal in the MMF-US trial which occurred at rates of 23%, 21%, and 26% in the Aza, MMF/2g/day, and MMF/3g/day cohorts, respectively [159].

Clinical Implications of Trial Data: Overview

The pivotal efficacy finding in both the MMF and FK clinical trials was that patients receiving MMF-Pred-CsA or FK506-Pred-Aza experienced a significantly lower rate and aggregate severity of acute rejection episodes compared to concurrent controls treated with CsA-Pred-Aza or CsA-Pred. Although qualified by unavoidable limitations of statistical significance, immunodeficient complications and nonimmune toxicities among patients receiving MMF- or FK506-based regimens were not prohibitively frequent or severe when compared to those encountered in the conventionally treated controls [54, 142, 159, 194, 195]. Despite this seemingly compelling "take-home" message, however, concerns related to both long-term cost and the timeless goal of optimizing the therapeutic index for each of our patients mandate consideration of the whys and the wherefores underlying the acute rejection data before subscribing to a paradigm that calls for uniform use of one or another of the "experimental" regimens utilized in the trials.

Acute Rejection Rates: Impact of CsA Pharmacokinetic Vulnerability

The most straightforward explanation for the lower incidence of acute rejection observed in the trial patients receiving Pred-CsA-MMF or Pred-FK506-Aza is that these combination therapies achieved a level of net immunosuppression sufficiently potent to suppress "homograft reactions" [112] too strong to be obviated by conventional CsA-based regimens. Consideration of the fixed CsA dosage protocols used in each of the trials renders it arguable, however, that susceptibility to acute immunologic injury among a substantial number of trial patients derived from inadequate CsA exposure, particularly during the very early post-transplant period. The protocols for CsA and FK506 dosing used in the trials, as well as pertinent background data addressing the issue of CsA pharmacokinetic vulnerability in the trial protocols are summarized in the following paragraph.

In the MMF-US study, protocol CsA doses ranged from 6.3 – 6.6 mg/kg/day from 0 – 28 days and, while adjusted to meet unspecified

center-specific target trough levels, remained in a relatively narrow range of 4.8 – 5.2 mg/kg/day at 6 months [159]. In contrast, the MMF-EUR trial participants initiated CsA at doses ranging from 5 – 15 mg/kg/day [194], while patients in the MMF-TRI study began CsA within 24 hours of transplantation at a dose of 3 mg/kg/day IV or 8 – 10 mg/kg/day orally (PO) [195]. CsA doses in the latter 2 studies were also adjusted to meet unspecified, center-specific trough level targets. Patients in the control arm of FK-EUR trial received CsA at an initial oral dose of 4 mg/kg twice daily with trough levels targeted at 100 – 300 ng/mL. CsA was initiated in the FK-US trial protocol at an oral dose of 5 mg/kg twice daily with trough level targets set in the range of 150 – 400 ng/mL for the first 3 months and 100 – 300 ng/mL, thereafter [142]. CsA levels were measured using either whole blood TDx or HPLC techniques in both FK506 studies [111, 142]. Of note, this important methodologic distinction was not factored into the data analyses. In contrast to the CsA dosage schedules, both the FK-US and FK-EUR studies targeted FK506 trough levels (all measured by the whole blood, IMx) in a relatively high range that encompassed values with demonstrated efficacy in the challenging immunologic milieu of refractory acute rejection [111, 142, 187].

The clinicopharmacologic implications inherent in the fixed CsA dosage protocols summarized above become rather obvious when one considers the interpatient variability in absorption and rate of elimination characteristic of the conventional preparation of CsA. Population studies have documented that values for these 2 important determinants of the adequacy of drug exposure range from 2 – 89% and 2 – 32 mL/kg/min in renal transplant recipients [76]. Additional evidence of the striking interindividual variability in drug exposure attending the use of fixed dosage schedules of the conventional formulation of CsA was documented in an analysis of 493 CsA pharmacokinetic profiles performed in 212 patients receiving a standardized Pred-CsA induction and maintenance protocol during the first post-transplant month [75]. Results included mean peak CsA levels and elimination half-lives ($t_{1/2}$) were 1087 ± 744 ng/mL (Sandoz, serum polyclonal RIA) and 9.6 ± 5.8 hours, respectively [75]. Similarly, 12 and 24 hour pharmacokinetic profiles performed in our center following initial oral doses of 7 mg/kg or 14 mg/kg, respectively, resulted in peak and trough concentrations (WB TDx) ranging from 337 – 3980 ng/mL and 103 – 1251 ng/mL, respectively [106]. These data provide strong support for the admonition, articulated by Kahan and Grevel [76], that "variations in [CsA] absorption, volume of distribution, and metabolism as estimated by clearance rates are so great that strategies based on median population values are not useful for a great proportion of patients. [As such,] it is necessary to devise a CsA strategy that tailors therapy to compensate for inter individual variations. . . [and] a dosing strategy that achieves uniform drug levels by compensating for pharmacokinetic variation is essential for . . . a rational CsA regimen".

Given the pharmacokinetic considerations summarized above and the clinical correlation between early CsA exposure and risk of acute rejection [106b], it is arguable that a substantial number of acute rejection episodes occurring in the conventionally treated trial patients may have been a consequence of inadequate exposure to CsA, particularly during the immediate post-transplant period when, as noted by Dr. Starzl more than 25 years ago, "the issue of graft acceptance or failure is most commonly decided" [164]. A clear corollary of this postulate is that the beneficial impact on acute rejection rates associated with en-

hancement of net immunosuppression attending substitution of MMF for Aza or replacement of CsA with FK506 within the context of the trial protocols may, for a substantial number of study subjects, reflect compensation for ineffective CsA dosing rather than overmatching alloimmune responses so intrinsically strong as to be invulnerable to conventional CsA-based regimens. Support for this contention is implicit in the benchmark acute rejection rates (< 20%) reported in association with antibody induction and conventional CsA-era maintenance regimens [19, 23, 45, 46, 72, 82, 106, 177].

One final consideration bearing on immunologic risk consequent to early CsA pharmacokinetic vulnerability is the frequency of laboratory monitoring and lengthening of the turn-around time between submission of blood specimens and actual dosage adjustments that accompanies transition from the inpatient to the outpatient setting. While the importance of protocol variability with regard to these 2 particulars of management seems self-evident, not accounting for them has been a traditional shortcoming of clinical outcome studies in renal transplantation.

Adverse Events

Scrutiny of the clinical trial data suggests that it may be somewhat premature to conclude that increasing the normative level of net immunosuppression by uniform use of MMF and/or FK506 will not increase the risk of clinically severe immunodeficient complications and/or nonimmune toxicities over that associated with conventional CsA-era regimens. Specific concerns in this regard include the paucity of specific information reflecting the clinical severity of opportunistic infections and nonimmune toxicities encountered in trial patients, relative rates of some serious complications (e.g. GI bleeding, PTDM, and DVT), the frequency of premature study withdrawal consequent to adverse events, and the incidence of septic deaths. This issue will become particularly important as the trial results inevitably lead to use of combination regimens that employ FK506 together with MMF.

Long-term Issues

A number of important questions have arisen related to potential benefits and disadvantages associated with the use of MMF or FK506 in the long-term, viz graft attrition, immunodeficient complications, and costs. The reader is referred to the review by Freund [38] for an excellent overview of basic methodologies used in pharmaco-economic analyses. With regard to the clinical issues, several questions are of obvious relevance to the risk-benefit equation concerning long-term use of combination maintenance therapies involving MMF and/or FK506. Will the aggregate increase in net immunosuppression afforded by such regimens result in a lower rate of allograft attrition caused by chronic rejection? Will it increase susceptibility to neoplastic or infectious diseases? Will outcome and cost analyses eventually indicate that the number of maintenance drugs can be reduced beyond the first 6 – 12 months following transplantation? Clearly, resolution of these issues will require more extended follow-up of patients involved in the MMF and FK506 clinical trials and other relevant studies. Finally, as experience accumulates with these new agents, other combination therapy options may emerge that set new benchmarks for broadening the therapeutic window in renal transplant recipients. In this regard, the short- and long-term issues associated with steroid reduction and withdrawal are being reexamined in the

context of protocols utilizing FK506, MMF, CsA-ME, and sirolimus in a variety of combination regimens.

MMF in Patients with Compromised Allograft Function

Rationale

One final consideration pertinent to MMF derives from both its lack of nephrotoxicity and more reliable efficacy compared to conventional doses of azathioprine. More specifically, MMF offers the promise of facilitating recovery of renal allografts with delayed graft function (DGF) and reducing the rate of functional attrition in patients with chronic renal allograft failure syndrome, while improving the risk of supervening acute immunologic injury over the conventional approaches of reduction or withdrawal of CsA.

Historically initial non-function has been associated with a reduction in the probability of 1-year graft survival ranging from 15 – 20% or greater, as well as an increased rate of attrition beyond one year [3, 9, 22, 26, 51, 171]. The pathophysiology of initial non-function is complex. A central role is played by acute vasomotor dysfunction that may be produced by varying combinations of harvest and preservation-related ischemia, post-ischemic reperfusion injury, local impact effects of the alloimmune response, and the acute renal vasomotor effects of CsA (or FK506) nephrotoxicity [5, 24, 62, 63, 92, 94, 101, 108, 122, 134, 135, 144, 145, 185]. In addition, ischemic injury may amplify the strength of the homograft reaction via up-regulation of local facilitators of the alloimmune response, e.g. endothelial cell surface expression of major histocompatibility complex (MHC) antigens and adhesion molecules [48, 154, 169]. The latter experimental findings are consistent with the clinical observation that acute rejection is diagnosed more frequently in the setting of DGF than in grafts with good initial function [51, 154, 169]. From a physiologic perspective, ischemia-reperfusion injury and acute CsA/FK506 nephrotoxicity may reduce renal reserve to an extent that renders the transplanted kidney relatively intolerant to the acute vasomotor dysfunction characteristic of the early phase of local immunologic injury, as described in both a canine model and human renal allografts by Hollenberg, Retik, and colleagues [62, 63, 144, 145]. Finally, preexisting disease process(es) intrinsic to the allograft, and compromised systemic hemodynamics during the intra- and post-operative periods are also of obvious relevance to the pathogenesis of initial non-function [24, 51].

The clinical importance of the relationship between initial non-function and immunologic outcome was recently affirmed by retrospective studies in which both the Universities of Minnesota and Wisconsin reported that neither short- nor long-term outcomes were compromised in patients with initial non-function when their clinical courses were rejection-free [110, 141, 172]. Nonetheless, graft arteriopathy has been documented to occur with significantly greater frequency in the setting of relatively marked, early ischemic injury, e.g. cadaveric vs. living donor source and cadaveric kidneys with prolonged cold ischemic times [9, 91]. A cause and effect relationship between severe ischemic injury and the development of chronic renal allograft arteriopathy has also been established in the experimental setting [48, 169, 173].

It follows from the above that, given the increase in renal vascular resistance uniformly attending exposure to therapeutic concentrations of CsA and FK506, there is clearly a need for alternative approaches to rejection

prophylaxis that more optimally promote the physiologic milieu necessary for recovery from extended periods of initial non-function and slow progression in patients with chronic renal allograft failure syndrome. The obvious question is whether short- and long-term clinical outcomes in these patients can be improved with the use of MMF (or, perhaps, sirolimus) along with Pred and no or markedly reduced doses of CsA or FK506. While not as yet addressed in controlled trails, conversion from CsA to MMF in the chronic setting has been reported to slow the aggregate rate of decline of renal allograft function without precipitating acute rejection episodes in a cohort of 28 patients followed for a mean of 24 ± 8 months [184].

Potential Pitfalls

While the rationale for use of MMF in the settings of delayed graft function and chronic progressive graft nephropathy is straightforward, caution is warranted as a consequence of the potential for severe renal insufficiency to narrow the therapeutic index of this potent antiproliferative agent. Both pharmacokinetic and pharmacodynamic considerations underlie this concern. With regard to the latter, relevant particulars include documentation that the clinical effects of MMF are mediated by unbound MPA and recent, prospective substantiation that the risk of acute renal allograft rejection declines as area under the total MPA concentration vs. time curve increases [178]. From a pharmacokinetic perspective, pertinent considerations include the following:

– the major metabolite of MPA, MPAG, is eliminated by renal excretion,
– MPAG reduces MPA protein binding in a concentration-dependent manner and, as such, levels of unbound MPA increase in proportion to those of MPAG, and
– like many acidic drugs, binding of MPA to albumin may be reduced purely as a consequence of severe renal dysfunction [133, 153].

The pharmacology of MMF, as summarized above, establishes a compelling case for the use of therapeutic drug monitoring in patients receiving this potent new agent, particularly those with compromised allograft function. Nonetheless, the clinical impact of monitoring the “free fraction” of total MPA concentration or absolute levels of MPA on the risk of immunodeficient complications and nonimmune toxicities has not been determined to date. Preliminary clinical data pertinent to the issue of therapeutic drug monitoring was recently provided by Kaplan et al. [83] in a case report documenting markedly elevated circulating levels of both MPAG and unbound MPA in an MMF-treated simultaneous kidney-pancreas transplant recipient with a non-functioning renal allograft who developed severe bone marrow suppression. This case study provides compelling affirmation of the importance of ongoing efforts to establish a scheme for therapeutic drug monitoring based on correlations between these pharmacokinetic parameters and adverse events [153a]. Pending development of a such a pharmacokinetic/pharmacodynamic paradigm, an added measure of caution is indicated in the use of MMF in patients with severe renal insufficiency.

Sirolimus (Rapa)

Sirolimus is a macrolide derived from the actinomycete *Streptomyces hydroscopicus*. Currently undergoing phase III clinical trials in the United States, Canada, and Europe, sirolimus is a structural analog of FK506 that suppresses the late phase of T cell activation

by interfering with the signaling process generated by the interaction between interleukin 2 (Il-2) and its cell surface receptor. Preclinical studies have also suggested that sirolimus induces the formation of blocking antibodies that promote allospecific tolerance [81]. A potentially unique impact on the development of tolerance was also suggested by experiments demonstrating that an abbreviated course of sirolimus administered in association with an antilymphocyte preparation and allospecific bone marrow infusion was substantially more effective than CsA in a primate kidney transplant model [49a].

The pharmacokinetic properties of sirolimus have been characterized in studies of stable renal allograft recipients [18, 79, 192]. Absorption is variable but rapid (T_{max} = 1.4 ± 1.2 hour) [192]. The elimination $t_{1/2}$ is quite long (62.3 ± 16.2 hours) and, as such, suggests that once-daily dosing will be adequate for most patients [192]. Importantly, a 4.5-fold interindividual variability in oral clearance rates mandates therapeutic drug monitoring. A very strong correlation between trough levels and area under the concentration-time curve has also been described [192]. Currently, high pressure liquid chromatography (HPLC) is used to measure blood levels of sirolimus and immunoassay techniques are under development [79]. One additional pharmacologic observation of potential clinical importance was that maximum concentration, trough, and area under the concentration-time curve for sirolimus were significantly increased by the simultaneous administration of CsA. This effect was obviated when the 2 drugs were administered 4 hours apart [83].

Early clinical trials reported acute rejection rates below 10% when sirolimus was administered in combination with the micro-emulsion preparation of CsA and corticosteroids [81]. Principal side effects have been thrombocytopenia and hyperlipidemia with the latter including elevation of both triglycerides and cholesterol [81]. Like FK506 and MMF, the ultimate role of sirolimus in the lexicon of immunosuppressive options will be determined on the basis of both final analyses of phase III clinical trials and experience acquired after the drug is released for general use.

Overview

Given the historical impact of acute rejection on short- and long-term outcomes, the most consequential implication of the MMF and FK506 trial results is that rational, contemporary maintenance immunosuppressive therapy mandates use of one or both of these new agents in all renal transplant recipients. On the other hand, interpretation of the trial data in relation to benchmark outcomes reported in other studies of patients receiving conventional CsA-based regimens suggests that the best approach to balancing considerations of safety, efficacy, and cost is likely to derive from an individualized approach to induction and maintenance immunosuppressive therapy rather than a “bandwagon” strategy in which a single agent or combination regimen is utilized in all patients.

The most obvious and demanding challenge inherent in taking an individualized approach to the contemporary management of renal transplant recipients abides in the formulation of a rational paradigm governing selection of one or another of the unprecedented number of options for combination immunosuppressive therapy made available by the introduction of the new drugs. It seems prudent to begin the quest for guidelines that will help in accomplishing this task with a return to the basic principles governing trans-

plantation biology as articulated by Medawar and summarized earlier in the present chapter. Of particular relevance to this task is the axiom that variability is a fundamental characteristic of the "homograft reaction". Quoting, once again, from the Croonian lecture, "[The] strong [reactions are]. . . sufficient to cause a homograft to break down in about 10 days, and the weakest those which may allow a homograft upwards of 100 days of grace before a reaction overtakes it" [112]. Amplifying on this theme, George Snell, another pioneering transplant biologist, wrote during the same year that ". . . the reaction may not be strong enough in all cases to cause graft rejection but . . . it is probably always present" [158].

Variability in the strength of the "homograft reaction" clearly implies that "one size does not fit all" with respect to the minimum level of 'net immunosuppression' required to achieve efficacy in the clinical setting. Clearly, patients mounting a relatively stronger alloimmune response against their grafts stand the most to gain from increasing the intensity of immunosuppression by employing FK506 and/or MMF. Unfortunately, however, contemporary immunologic monitoring techniques have not provided a consistently reliable means for a priori determination of the level of immunosuppression required to offset the intrinsic strength of an individual homograft reaction on a proportionate basis [87]. Nonetheless, it is arguable that use of newer, more potent regimens as a means to compensate for suboptimal early CsA exposure may unnecessarily narrow the short- and long-term therapeutic windows established in benchmark, conventional CsA-era outcome studies involving the use of antibody induction, preemptive ganciclovir, and judicious use of therapeutic drug monitoring to insure continuously effective circulating concentrations of CsA, particularly during the critical early post-transplant period. Added risks of short- and long-term immunodeficient complications that are likely to accompany escalation of normative levels of net immunosuppression attending uniform use of MMF and/or FK506 also speak to the utility of an individualized approach to therapy that encompasses use of conventional CsA-based regimens.

Individualization of contemporary immunosuppressive therapy clearly demands the exercise of clinical judgement based on familiarity with the patient, the physiologic status of the allograft, and evolving information related to the safety, efficacy, and cost-effectiveness of different therapeutic options. In this regard, neither market forces nor the impressive size of pioneering, multicenter clinical trials should dissuade clinicians from evaluating trial outcomes in relation to historical and current benchmarks established at their own centers as well as in the literature.

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Allograft Dysfunction: Differential Diagnosis and Management

Colm C. Magee and Mohamed H. Sayegh

Introduction

Despite improvements in surgical techniques, human leukocyte antigen (HLA) typing and immunosuppressive regimens, allograft dysfunction remains the most common complication of renal transplantation. The causes of allograft dysfunction depend on the time period after transplantation, allowing a rational diagnostic and therapeutic approach in many cases. Time periods are considered here as

- immediately post-transplant,
- early (1 – 12 weeks) post-transplant, and
- late (> 3 – 6 months) post-transplant but there is obviously some overlap in causes between these periods.

Immediate Post-transplant Period – Delayed Graft Function

Delayed graft function (DGF) is usually defined as failure of the renal allograft to function immediately post-transplant, with the need for one or more dialysis sessions within a specified period, typically one week. It is important to note that this is a *clinical* diagnosis. Using requirement for dialysis as the sole criterion for diagnosis excludes some patients with residual native kidney function, however. Reported rates of DGF from recent series in patients receiving cadaveric kidney transplants are 9 – 25% [67, 116]. Use of non-heart beating donors is generally associated with a higher incidence of DGF [6, 139]. Although ischemic acute tubular necrosis (ATN) is by far the most common cause of delayed graft function, the 2 terms are not synonymous. Review of the relevant literature is complicated by the terms being used interchangeably. There are several other causes of DGF (Table 1); in addition ischemic and immunological injury may co-exist.

Table 1. Causes of Delayed Graft Function

Prerenal
Severe hypovolemia/hypotension
Renal vessel thrombosis
Intrarenal
Ischemic ATN (most common)
Hyperacute rejection (rare)
Accelerated or acute rejection superimposed on ATN
Acute cyclosporine nephrotoxicity (with or without ATN)
Postrenal
Urinary tract obstruction/leakage

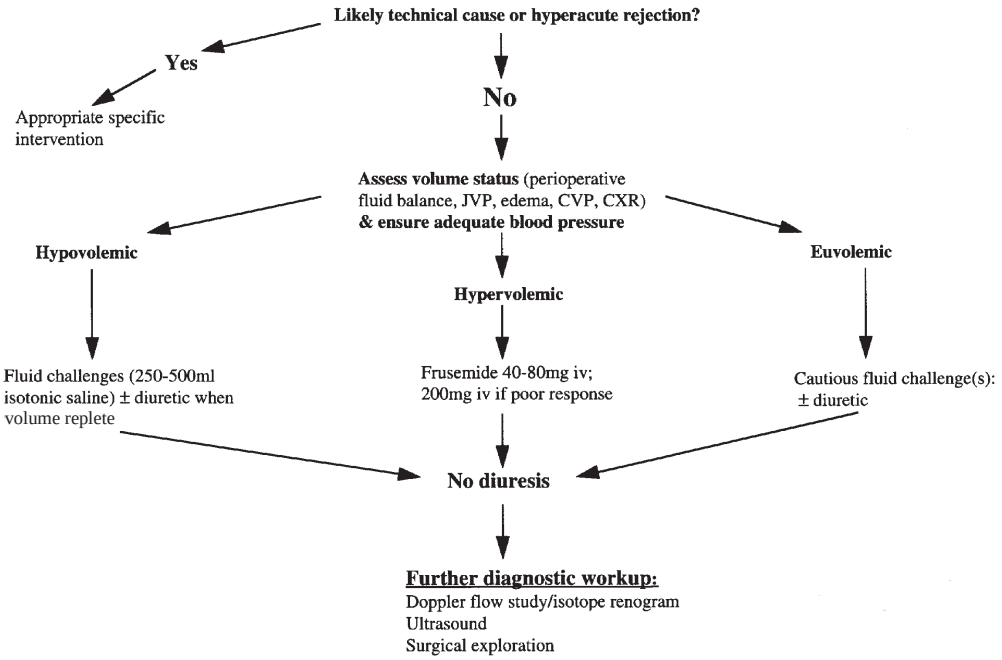
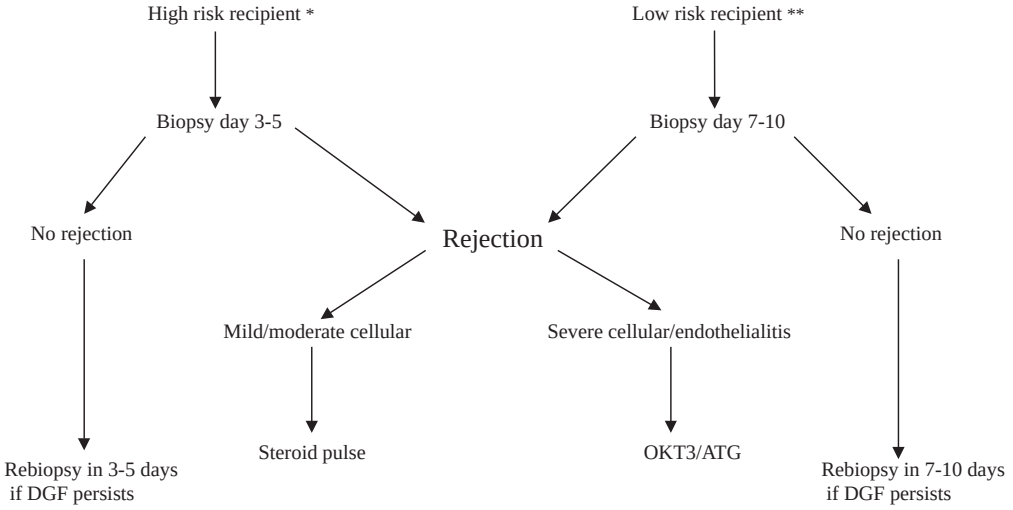


Figure 1. Management of graft non-function/oliguria immediately post-transplant.

Risk factors for DGF include donor age (> 50 years) [102], prolonged cold ischemia times [94], prolonged anastomosis time [120], intraoperative or postoperative hypovolemia / hypotension, initial high cyclosporine (CsA) levels [40] and sensitized or previously transplanted recipients [115]. Many of these factors act by increasing the risk of ischemic damage and therefore ATN but the last factor supports an underlying immunological etiology in some cases. In < 5% of cases, allografts with delayed function never recover: these are said to have primary non-function. In the case of kidneys from non-heart beating donors, macroscopic and microscopic examination is used to exclude organs severely damaged by ischemia; rates of primary non-function may then approach those of grafts from heart beating donors [139].

Clinical, radiological and often histological findings are used to diagnose the underlying causes of DGF. An algorithm for the management of transplant kidney non-function/oliguria immediately after surgery is shown in Figure 1. The donor history and the harvesting and transplantation process must be carefully reviewed as they often provide clues to the etiology of DGF. Note that interpretation of the urine output requires knowledge of the pre-transplant native kidney output. Prerenal and postrenal causes (including simple problems such as urinary catheter malposition or obstruction) must always be considered. Response to a fluid challenge implicates prerenal factors. If optimization of volume status and administration of diuretics fails to improve renal function, further investigation is warranted. The urgency with which further investigations are undertaken will depend on the individual case. For example, persistent oliguria of a living donor kidney despite hydration and administration of high



* Sensitised/previous transplant etc.

**More likely to be ischemic ATN

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Figure 2. Algorithm for diagnostic biopsy and treatment of persistent DGF.

dose loop diuretics requires immediate radiological evaluation of renal blood flow (by doppler flow study and/or radionuclide scan) or even immediate surgical re-exploration since the cause of impaired function is more likely to be a major surgical complication than ATN. On the other hand, a cadaveric kidney from an elderly donor and with prolonged ischemia times might be expected to suffer some delayed function from ischemic ATN (see below).

Ultrasound evaluation is very useful as it inexpensive, non-invasive and effective in excluding postrenal causes. Doppler flow studies are useful for assessing renal arterial and venous blood flow but cannot reliably distinguish intrarenal causes based on changes in intrarenal vascular resistance [99]. Nuclear medicine imaging may provide additional information. Absent renal blood flow suggested by doppler studies is best confirmed by isotope renography. Occasionally, the presence of a urine leak or urinary tract obstruction is detectable by renography but not by initial ultrasonography. Although changes are seen on the radionuclide scan with intrarenal insults such as ATN or rejection, reliably distinguishing these is again not possible.

In many cases, prerenal and postrenal causes are excluded and the radiological abnormalities are consistent with an intrarenal insult. Definitive diagnosis requires allograft biopsy but many clinicians try to avoid biopsy until at least 5 days post-transplant. The decision to biopsy will depend mainly on the duration of DGF, the likelihood of the underlying cause being ATN and the risk of rejection. An algorithm for diagnostic biopsy and treatment of persistent DGF is shown in Figure 2. Specific treatment of DGF will obviously depend on the underlying cause (see below).

Ischemic Acute Tubular Necrosis

Ischemic ATN is the most common cause of DGF in cadaveric kidney transplant recipients. As noted above, ATN is unusual in living donor grafts. The etiology of ATN in transplanted kidneys is presumed to be similar to that in native kidneys. At multiple steps during the surgical transplantation procedure the cadaveric graft is at risk of ischemic damage (Table 2). Reperfusion injury via direct endothelial trauma, oxygen free radical damage, neutrophil activation and other mechanisms is important also [50, 121]. Interactions between the graft endothelium and host neutrophils via ligands such as platelet activating factor (PAF) and adhesion molecules play an important role in local neutrophil activation. Spontaneous resolution of ATN usually occurs from 5 – 10 days post-transplant but ATN may persist for weeks. As is the case with acute renal failure (ARF) in native kidneys, transplant ATN should be a diagnosis of exclusion. Several of the risk factors identified in Table 2 may be present. Histology, if available, shows tubular cell damage and necrosis similar to that found in native kidneys with ATN although Solez has noted that transplant tubular necrosis is much more overt [124]. Patchy interstitial lymphocytic infiltrates but not tubulitis may be present.

Treatment is essentially supportive: avoidance of fluid overload; nutritional support and dialysis as needed. Intravenous (IV) calcium gluconate and glucose/insulin can be used with some effect to treat hyperkalemia and thus temporarily postpone dialysis. Kayexalate is contraindicated in the early postoperative period because of the risk of colonic dilation and perforation [100]. Minimum anticoagulation protocols should be used during hemodialysis (HD). Care should be taken to avoid intradialytic hypotension which risks worsening graft damage. Although there is little direct evidence for the superiority of biocompatible over bioincompatible HD membranes in the setting of post-transplant ATN, many centers routinely use biocompatible membranes. In fact, one small prospective trial found no benefit in this setting [132]. Peritoneal dialysis (PD) is probably best avoided in the first week post-transplant because of the risk of peritonitis or leakage of dialysis fluid into the wound area, but dialysis treatment should be tailored to the individual patient.

Table 2. Causes of Ischemic Damage to the Cadaveric Renal Allograft

1. Preharvest donor state
Shock syndromes
Endogenous and exogenous catecholamines
Nephrotoxic drugs
2. Organ procurement surgery
Hypotension
Trauma to renal vessels
Inadequate flushing
3. Organ transport and storage
Prolonged storage (cold ischemia time)
Pulsatile perfusion injury
4. Transplantation of recipient
Prolonged second warm ischemia time
Trauma to renal vessels
Hypovolemia/hypotension
5. Postoperative period
Cyclosporine

A major concern is that clinical and laboratory evidence of new-onset surgical or medical complications involving the graft is rarely apparent in patients with severe ischemic ATN. Acute or accelerated acute rejection may therefore easily be missed. In fact, acute rejection occurs more frequently in grafts with delayed as opposed to immediate function [94]. The postulated mechanism is that

ischemic and reperfusion injury increase the "immunogenicity" of the graft and thereby predispose to acute rejection. Experimental animal models have demonstrated that ischemic ATN is associated with increased expression/production within the renal parenchyma of major histocompatibility complex (MHC) class I and II molecules, costimulatory molecules, proinflammatory cytokines and adhesion molecules [51, 126]. Such an altered local milieu would amplify alloimmune responses. Indirect evidence for the importance of these mechanisms in human transplantation is that poorer HLA matching accentuates the detrimental effect of DGF on allograft survival [122].

Radiological evaluation of the graft should be repeated regularly to detect new urinary or vascular complications. In some centers, core kidney biopsies are repeated in patients with prolonged ATN (Figure 2). Because of the small risk and inconvenience associated with core kidney biopsy, sequential fine needle aspirates have been recommended as an alternative but interpretation requires expertise generally available in only a few centers and the technique in not widely practised [16]. There is also concern that vessel involvement by rejection (see below) may be underdiagnosed by fine needle aspiration.

In the case of DGF secondary to ischemic ATN, an initial induction immunosuppression regimen with anti-thymocyte globulin (ATG) or OKT3 substituted for full dose CsA has been advocated [14] (see chapter III-4). This has the theoretical benefit of preventing CsA nephrotoxicity while reducing the risk of occult rejection in the non-functioning graft. Use of induction therapy is expensive and increases the risk of serious infection, particularly cytomegalovirus (CMV). Recent analysis of the United Network for Organ Sharing (UNOS) Scientific Renal Transplant Registry showed that use of antibody induction protocols significantly reduced the incidence of early acute rejection in recipients with DGF; no improvement in 1 or 3 year graft survival or graft half-life was seen, however [61].

Hyperacute Rejection

Besides ABO blood group incompatibility, hyperacute rejection is caused by preformed recipient anti-HLA class I antibodies crossreacting with antigens on the endothelial surface of the allograft and hence activating the complement and coagulation cascades. These anti-HLA class I antibodies are formed in response to previous transplantation, blood transfusion or pregnancy [115]. Rarer causes of hyperacute rejection are mediated by anti-HLA class II antibodies (associated with a positive B cell crossmatch) or anti-donor endothelial/monocyte antibodies. Macroscopic changes may be seen minutes after vascular anastomosis is established. Clinically there is cyanosis and mottling of the kidney, anuria and occasionally disseminated intravascular coagulopathy (DIC). Radiological studies confirm absent or minimal renal perfusion, in contrast to ATN where blood supply is relatively well maintained. Histology shows widespread small vessel endothelial damage and thrombosis, usually with neutrophil polymorphs incorporated into the thrombus (Figure 3). Similar histological findings may occur with pulsatile perfusion injury, cryoglobulinemia, DIC, or fat emboli. The time course and the presence of neutrophil polymorphs within the thrombi are helpful in distinguishing hyperacute rejection from these other lesions. There is currently no effective treatment and transplant nephrectomy is indicated. Fortunately, hyperacute rejection is now a rare cause of primary graft non-function because screening for recipient-donor AB0 blood group or class I MHC incompatibility (the

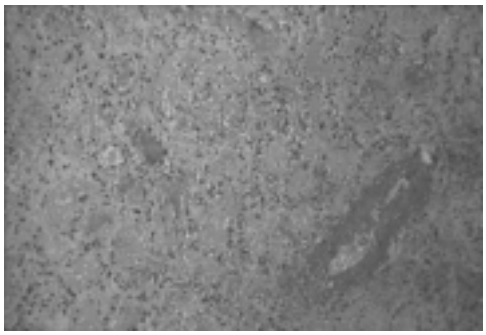

Figure 3. Hyperacute rejection: There is fibrinoid necrosis of the wall of the interlobular artery and coagulative necrosis of the tubules and glomeruli. Although not seen clearly here, incorporation of polymorphic neutrophils into the thrombus is characteristic. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

presence of the latter is often referred to as a "positive T cell crossmatch") identifies most potential cases. Rare cases occur because of clerical errors or due to the presence of the other preformed antibodies described above which are not detected by routine screening methods. Anti-donor endothelial/monocyte antibodies may cause a delayed onset hyperacute rejection syndrome in HLA identical grafts.

Accelerated Rejection Superimposed on ATN

Accelerated acute rejection refers to rejection episodes occurring between days 2 and 5 post-transplant. Pre-transplant sensitization of the recipient to donor alloantigens is thought to be the cause. This arises from previous transplantation or, less commonly, blood transfusion. Associated immunological findings include an occult positive T cell crossmatch, a positive B cell crossmatch or a positive flow cytometry crossmatch in re-transplanted patients. Accelerated acute rejection may be superimposed on ischemic ATN in which case there may be no signs of rejection or it may occur in an initially functioning allograft. Diagnosis is by renal biopsy which usually shows predominantly antibody rather than cell mediated immune damage [26]. The classic finding is necrotizing arteritis: "fibrinoid" necrosis and inflammation of the arterial wall. Immunofluorescence shows that the fibrinoid material contains immunoglobulin, complement and fibrin. Patients with presumed ischemic ATN who are at high risk (e.g. sensitized by previous transplantation) of developing this form of rejection should undergo biopsy 3 to 5 days after transplantation. First-line treatment for accelerated acute rejection is either high dose steroids or OKT3. Overall, the prognosis for recovery of good allograft function is guarded.

Acute CsA / Tacrolimus (FK506) Nephrotoxicity Superimposed on ATN

CsA, especially in high doses, causes an acute reversible decrease in GFR by renal vasoconstriction, particularly of the afferent glomerular arteriole [68]. This is discussed in more detail below. DGF may occur in severe cases, particularly if underlying ischemic ATN is present.

Vascular and Urological Complications of Surgery

Renal vessel thrombosis, urinary leaks and obstruction are rarer but important causes of DGF. These complications may also cause

allograft dysfunction in the early postoperative period and are discussed briefly below and in more detail in Chapter III-3.

Significance of Delayed Graft Function

Patients with DGF require longer hospitalization, more interventional studies and are at higher risk of occult rejection or other undiagnosed insults to the graft. Postoperative fluid and electrolyte management is more difficult. Health care costs are substantially increased; the annual cost of DGF in the US has been estimated at $54 million [94]. Although the majority of patients become independent of dialysis, most recent studies have demonstrated that recipients with DGF have poorer long-term graft outcome compared to those without DGF [61, 67]. Whether or not this effect is mediated by immune mechanisms (the increased risk of rejection), non-immune mechanisms or both is disputed. Several authors have argued that ATN in the absence of rejection has no impact on long-term cadaveric graft survival [51, 129]. However, a recent analysis of primary cadaveric renal transplant outcome from the US Renal Data System (USRDS) performed between 1985 and 1992 showed that DGF was an *independent* predictor of 5-year graft loss (relative risk = 1.53). The additional presence of acute rejection had an additive adverse effect with a 5-year graft survival of only 35% [94]. The importance of ischemic injury is indirectly illustrated by the impressive graft survival outcomes in living non-related donor transplantation where ischemia times are much shorter [22].

Measures to limit the incidence and duration of DGF are therefore very worthwhile. Strategies include optimization of donor status and appropriate intraoperative volume expansion of the recipient. Intraoperative administration of mannitol may be of benefit [67, 138]. Invasive vascular monitoring is useful for titrating fluid administration. Systolic blood pressure should be maintained > 120 mmHg. Meticulous surgical technique, rapid transport of harvested grafts and use of optimum preservation solutions are of obvious extreme importance. Use of University of Wisconsin preservation solution during the cold ischemia period reduces the incidence of DGF [102] and its use is now standard practice in most centers. Whether or not machine perfusion of cadaveric renal allografts is more effective than simple cold storage in preventing DGF remains controversial. It is certainly more expensive and complex. Prospective controlled trials where one kidney from each donor is allocated to machine perfusion and the other to cold storage (thus controlling for donor factors) have yielded conflicting results [3, 84]. There is evidence that machine perfusion of grafts from non-heart beating donors lowers the incidence of DGF [30]. If kidneys from marginal ("expanded criteria") donors are being used, transplantation of both kidneys into one recipient might be expected to lower the risk of DGF (see also below); 2 small studies have in fact shown a benefit with this strategy [2, 57].

The benefits and risks of induction therapy with OKT3 or ATG in the setting of ATN have been discussed briefly here. Calcium channel blockers have been shown in experimental models to prevent ischemic injury [15] and ameliorate CsA-mediated vasoconstriction. These properties suggested that administration of calcium channel blockers to cadaveric kidney transplant recipients in the perioperative period or to the donors before organ harvesting might reduce the incidence and/or duration of ischemic ATN. Unfortunately studies have produced conflicting results [71, 92]. Perioperative administration of dopamine to

the recipient is of no benefit [36]. Atrial natriuretic peptide (ANP) has been of limited benefit in the setting of non-transplant ATN [4] and is therefore unlikely to find use in the transplant situation. Strategies based on preventing neutrophil mediated reperfusion injury by blocking PAF-PAF receptor or adhesion molecule interactions are under investigation. BN 52021, a PAF antagonist significantly reduced the incidence of DGF in a pilot study in human cadaveric renal allograft recipients [49].

The benefits of pursuing better HLA matched cadaveric kidneys at the possible expense of prolonging transportation and cold ischemia times remain controversial. Another way of phrasing this conundrum: is a "fresh" kidney better than a well-matched one? Some have recommended disregarding HLA matching in an attempt to shorten cold ischemia time [10]. Studies, however, have shown only a small increase in cold ischemia time (2.5 hours) in better-matched compared to poorer matched allografts [54, 94]. Multiple organ retrieval (with the kidney often left until last) does not appear to be associated with an increased risk of renal DGF [67]. There is potential for further reduction in cold ischemia times as recent UNOS data show cold ischemia times > 24 hours in 40% of first cadaveric kidney transplants [45]. In any event, delayed graft function from ATN is likely to remain a significant problem in cadaveric kidney transplantation as the use of "marginal" donors continues to increase.

Table 3. Causes of Early Allograft Dysfunction

Prerenal
Hypovolemia/hypotension
Renal vessel thrombosis
ACE inhibition
Transplant renal artery stenosis
Intrarenal
Acute rejection (most common)
Acute cyclosporine/FK506 nephrotoxicity
Cyclosporine/FK506 induced thrombotic microangiopathy
Recurrence of primary disease
Acute pyelonephritis
Acute interstitial nephritis
Postrenal
Urinary tract obstruction/leakage

Early Post-transplant Period

Table 3 shows the causes of allograft dysfunction during the early (1 – 12 weeks) post-transplant period. There is obviously some overlap in the causes of delayed and early allograft dysfunction. Despite its known limitations, the primary measure of early and late transplant function remains the plasma creatinine. Large elevations in plasma creatinine (> 25% over baseline) usually represent a significant, potentially graft-endangering event. Again, prerenal failure should always be excluded and renal ultrasound performed to exclude postrenal causes.

Prerenal Dysfunction

Hypovolemia may develop secondary to high volume diuresis from the transplanted kidney or from "third space" losses. In cases resistant to fluid resuscitation with falling hematocrit values, graft related bleeding must be considered. Angiotensin converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) should gener-

ally be avoided in the early post-transplant period because of the risk of functional prerenal failure with the often fluctuating volume status; this risk may be enhanced by the renal vasoconstrictive effects of CsA.

Renal Vessel Thrombosis

Renal artery or renal vein thrombosis usually occurs in the first 72 hours but may be delayed for up to 10 weeks post-transplant. Acute vascular thrombosis is the most common cause of graft loss in the first post-transplant week [97]. Renal artery thrombosis presents with abrupt onset of anuria (unless there is a native urine output), rapidly rising plasma creatinine but often little localized graft pain or discomfort. Doppler flow studies show absent arterial and venous blood flow. Scintiscans show absent perfusion and absent visualization of the transplanted kidney. Removal of the infarcted kidney is indicated.

Renal vein thrombosis also presents with anuria and rapidly increasing creatinine. Pain, tenderness and swelling in the graft and hematuria are usually much more pronounced than in renal artery thrombosis. Life-threatening complications such as embolization or graft rupture and hemorrhage may occur. Doppler flow studies show absent renal venous blood flow and characteristic highly abnormal renal arterial signals [144]. Again, transplant nephrectomy is indicated. If the venous thrombosis extends beyond the renal vein, anticoagulation is necessary to reduce the risk of embolization [83, 131]. There are case reports of salvaging renal function after early diagnosis of renal vessel thrombosis and intervention with thrombolysis [24, 114] or thrombectomy [25]. In almost all cases however, infarction occurs too quickly to make this treatment worthwhile. Thrombolysis is a high risk strategy soon after transplantation because of the high risk of graft related bleeding.

Meticulous surgical technique and avoidance of recipient hypovolemia will minimize the incidence of this devastating complication. Use of the low molecular weight heparin, enoxaparine, significantly reduced the incidence of graft thrombosis in one study of pediatric recipients [18]. The risk of postoperative bleeding in the enoxaparine group was high, however and few centers routinely anticoagulate all transplanted patients. Renal vessel thrombosis is further discussed in chapter III-3.

Intrarenal Dysfunction

Acute Rejection

Acute rejection is defined as an acute deterioration in renal allograft function associated with specific pathological changes in the graft. The reported incidence of acute rejection varies between centers, reflecting differences in patient case mix and immunosuppressive regimens. With regard to recipients of a first cadaveric kidney transplant, use of the "traditional" CsA/azathioprine (Aza)/ steroid regimen alone is associated with an approximate 40 – 50% risk of acute rejection in the first 6 months but this risk is significantly reduced (to approximately 20%) with the use of mycophenolate mofetil (MMF) based regimens [61]. Acute rejection is presumed to be secondary to both cell and humoral mediated immune responses but evidence of cell mediated responses predominates on most biopsies. In addition to an increasing plasma creatinine, common clinical signs are oliguria, hematuria and increasing proteinuria. A raised plasma creatinine is a relatively late marker of pathological changes occurring within the graft. Fever and symp-

Table 4. Diagnostic Categories for Renal Allograft Biopsies (Banff Criteria)

1. Normal

2. Hyperacute rejection

3. Borderline changes ("very mild acute rejection"). No intimal arteritis, only mild or moderate focal mononuclear cell infiltration with foci of mild tubulitis (1 – 4 mononuclear cells/tubular cross section).

4. Acute reiection
Grade I: mild acute rejection [cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells)]

Grade II: moderate acute rejection [cases with A: significant interstitial infiltration and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section) and/or B: mild or moderate intimal arteritis]

Grade III: severe acute rejection [cases with severe intimal arteritis and/or transmural arteritis with fibrinoid change and necrosis of medial smooth muscle cells. Or recent focal infarction and interstitial hemorrhage without other obvious cause.

5. Chronic allograft nephropathy. Graded as mild/moderate/severe (I/II/III) chronic transplant nephropathy, interstitial fibrosis and tubular atrophy

6. Other (changes not considered to be due to rejection)

Reproduced with permission from *Solez K et al.* 1993 International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int *44:* 411 – 422.

toms localized to the graft are uncommon in CsA-treated patients. The presence of fever requires that underlying infection be systematically outruled. Renal scintiscan, ultrasound and doppler flow studies are usually abnormal in acute rejection but the changes are not specific enough to exclude other causes [48]. Definitive diagnosis requires biopsy but where there is a high likelihood of uncomplicated acute rejection, empirical treatment is often instituted.

The Banff classification (Table 4) is a widely used schema for grading histological signs of renal allograft rejection and is useful in comparing the effects of different strategies on acute rejection [123]. The classical histological findings in acute cell-mediated rejection are:

– edema and mononuclear cell infiltration of the interstitium, mainly with CD4+ and CD8+ T lymphocytes but also with some macrophages and plasma cells, and
– tubulitis (infiltration of tubular epithelium by lymphocytes).

A typical example is shown in Figure 4. Glomerular involvement is rare but vascular involvement is common if sought carefully [26]. The latter reflects more severe rejection and is termed endothelialitis or arteritis. Here, mononuclear cells undermine endothelium (but rarely extend into the muscularis) and the endothelial cells are swollen and detached (Figure 5). Endothelialitis is frequently a focal process and may therefore be easily missed on biopsy. The term "vascular

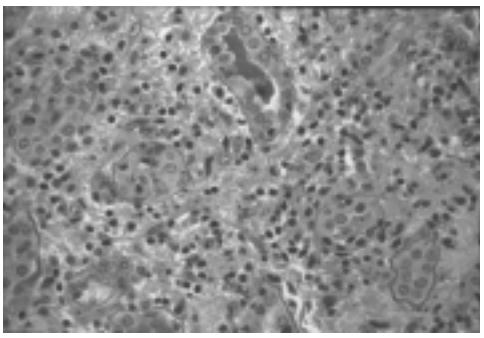

Figure 4. Acute cellular rejection: The interstitium is edematous and has a mononuclear inflammatory cell infiltrate. Tubulitis is present, i.e. mononuclear cells extend into the walls and lumina of the tubules with associated degeneration of tubular eptithelial cells. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

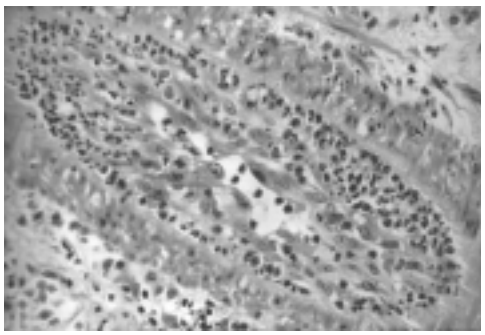

Figure 5. Acute rejection with arteritis/endothelialitis. There is a mononuclear and polymorphonuclear cell infiltrate in the expanded intima of the artery. There is severe endothelial damage and narrowing of the vessel lumen. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

rejection" is best avoided as it fails to distinguish between cell-mediated vascular damage (endothelialitis) and humoral-mediated vascular damage (necrotizing arteritis). The former is much more responsive to anti-rejection treatment than the latter [26].

Biopsy findings will be modified by prior treatment with anti-rejection drugs. It is also important to note that focal infiltrates of mononuclear cells without endothelialitis or tubulitis may occur in the presence of stable allograft function. Neutrophil infiltration is unusual and should suggest the alternative diagnosis of infection.

Uncomplicated acute cellular rejection is generally treated with a short course of high dose steroids – so called "pulse" treatment. Urinary tract infection (UTI) must always be excluded before instituting anti-rejection treatment. OKT3 or ATG are highly effective in treating first rejection episodes, reversing them in approximately 90% of cases [1, 35, 74]. Because of cost and toxicity, these agents are usually reserved for steroid-resistant cases or when there is severe rejection on the initial biopsy. Typically 500 – 1000 mg/day of methylprednisolone are given IV for 3 – 5 days [47, 135]. There is an approximate 70% response rate to this regimen. The main complication of such high dose steroid therapy is an increased risk of infection. After completion of pulse therapy, the maintenance oral steroid dose can be resumed immediately although some centers prefer to taper back to the maintenance dose. CsA/FK506 dosage should be increased if blood levels are "low".

Steroid-resistant acute rejection cases, defined somewhat arbitrarily as failure of improvement in urine output or plasma creatinine within 5 days of starting pulse treatment,

are usually treated with OKT3 or ATG. If steroid treatment was based on an empirical rather than a histological diagnosis of acute rejection, a biopsy is recommended before anti-T cell antibody treatment to confirm this diagnosis. The response rate to OKT3 in these situations is 80 – 90% [46]. Similar results are obtained with ATG [88].

If there is severe rejection with endothelialitis on the initial biopsy, OKT3 is often used as first line treatment as it is felt to be the most effective agent. The most important adverse effects of monoclonal or polyclonal antibody treatment, namely the increased risk of life-threatening infections and lymphoproliferative disease, are well known and should prompt careful analysis of the risks and benefits associated with their use in the treatment of aggressive rejection. Rebound rejection after OKT3 therapy occurs in approximately 50% of cases but this is usually mild and reverses in about 75% of such cases with pulse steroids.

Refractory Acute Rejection

Refractory acute rejection is generally defined as persistent rejection resistant to a course of OKT3. Therapeutic options include a repeat course of OKT3, switching from CsA to FK506 or switching from Aza to MMF. Encouraging results have been reported with switching to FK506 [141] and, to a lesser extent, to MMF [31]. If repeat courses of OKT3 are used, the dosage may need to be increased in patients who produce neutralizing anti-mouse antibodies.

Significance of Acute Rejection

Although acute rejection is frequently reversed (at least as assessed by plasma creatinine) retrospective studies show that it remains a major predictor of the development of chronic allograft nephropathy and is associated with poorer allograft survival [81]. This is discussed in more detail below. Poorer outcome has also correlated with the severity of rejection, the number of rejection episodes and with resistance to steroid therapy. Whatever the outcome, treatment involves exposing the patient to supplemental and potentially life-threatening immunosuppression.

Reducing the risk of acute rejection remains a major goal in transplantation. Fortunately, the incidence is decreasing over the last 20 years, mainly because of improvements in immunosuppression. CsA has been the major factor in this regard. Prophylactic use of OKT3/ATG is effective in decreasing the incidence of *early* acute rejection but is expensive and later rejections may occur more frequently [61]. In 3 recent randomized multicenter trials, MMF has been shown to reduce the incidence of early acute rejection after renal transplantation by almost 50% [133] and many centers now use this drug routinely in place of Aza. FK506 was more effective than CsA in preventing acute renal allograft rejection in 2 recently published multicenter trials [82, 101]. No significant improvement in short-term patient or graft survival was found with either drug but this is difficult to demonstrate with the current high one-year patient and graft survival rates. Analysis of the effects of these drugs on long-term outcome is awaited (see chapter III-4).

Acute CsA / Tacrolimus (FK506) Nephrotoxicity

CsA, especially in high doses, causes an acute reversible decrease in glomerular filtration rate (GFR) by renal vasoconstriction, particularly of the afferent glomerular arteriole

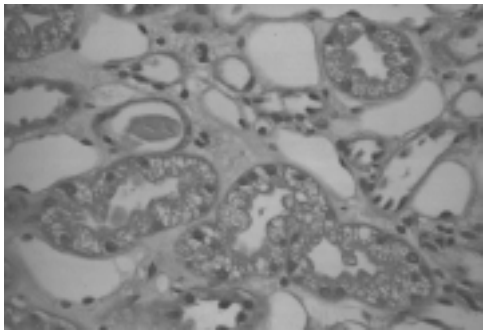

Figure 6. Acute cyclosporine nephrotoxicity. This slide of outer medulla shows marked vacuolization of tubular epithelial cells. Tubulitis is absent. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

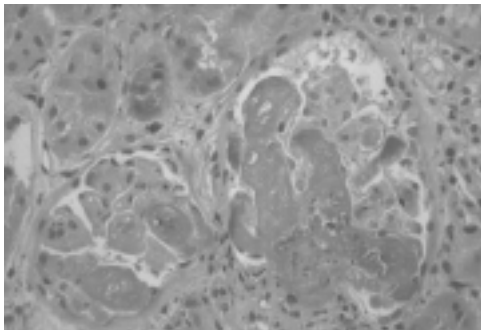

Figure 7. Thrombotic microangiopathy. Two glomeruli show extensive capillary thrombosis but no inflammation. Further thrombotic lesions may occur in arterioles and small arteries. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

[105]. This is manifested clinically as dose-dependent and blood level-dependent acute reversible increases in plasma creatinine. As acute CsA/FK506 nephrotoxicity is mainly vasomotor/prerenal, it is not surprising that the histological changes in this setting may be unimpressive. With very high CsA levels, direct proximal tubular damage and dysfunction may occur. This is not as commonly seen in the last 10 years because of the lower doses of CsA employed [124]. In such cases, histology shows tubular dilation, tubular cell flattening and scattered individual tubular cell necrosis. Giant mitochondria and isometric vacuolization in tubular cells reflect more severe damage (Figure 6). Hyaline thickening of arterioles is felt to be a more specific finding [124]. Acute CsA nephrotoxicity will respond to dosage reduction. FK506 causes a similar syndrome of vasomotor acute renal dysfunction and the guidelines above can broadly be applied to patients receiving this drug instead of CsA.

Thrombotic microangiopathy (TMA) after renal transplantation is a rare but serious complication. CsA and FK506, as well as other factors, have been associated with development of this syndrome, which is presumed to be initiated by direct endothelial damage [32]. Onset is usually in the early post-transplant period. The classical laboratory findings are an increasing plasma creatinine and lactate dehydrogenase (LDH), thrombocytopenia, falling hematocrit and the presence of schistocytes on the blood film. The hematological features of thrombotic microangiopathy may easily be missed, however. Renal biopsy shows platelet and fibrin thrombi in the lumina of arterioles and glomerular capillaries (Figure 7). Similar histological changes occur in cases of malignant hypertension, recurrent hemolytic uremic syndrome, pulsatile perfusion injury and hyperacute rejection. Early diagnosis of TMA is essential to salvage worthwhile renal function. Treatment involves cessation of CsA/FK506, control of

any hypertension present and plasma exchange. Prognosis for the allograft is poor although in one retrospective series of 13 cases, a regimen of temporary discontinuation of CsA/FK506, and the institution of aspirin, isradipine and pentoxifylline gave an initial response rate of 69% [143]. Long-term graft function (creatinine clearance) remained inferior to non-affected controls. Absence of recurrence after initial treatment has been reported with both reintroduction of CsA and switching from CsA to FK506 [63, 143].

Distinguishing Acute CsA/Tacrolimus (FK506) Nephrotoxicity and Acute Rejection

Unfortunately, even with the aid of blood drug levels, distinguishing acute CsA nephrotoxicity and acute rejection clinically can be difficult. Low and high CsA blood levels in the presence of deteriorating renal function suggest but do not imply rejection and drug nephrotoxicity respectively. Both syndromes may coexist. Pointers towards a diagnosis of acute CsA nephrotoxicity are signs of extrarenal toxicity such as severe tremor, a "moderate" increase in plasma creatinine (< 50% over baseline) and high CsA levels (> 350 ng/mL in whole blood). Pointers towards a diagnosis of acute rejection are fever, allograft pain and swelling; rapid, non-plateauing increases in plasma creatinine and low CsA levels (< 150 ng/mL in whole blood). Oliguria occurs in severe acute rejection but is rarely a feature of CsA toxicity. Sodium retention and edema may occur with either condition. Fever and symptoms localized to the allograft do not occur in CsA toxicity but by no means imply rejection: infections such as acute pyelonephritis must be considered. A false positive diagnosis of CsA toxicity in the presence of rejection followed by attendant incorrect treatment (lowering of CsA dosage and withholding of anti-rejection therapy) is potentially much more deleterious than a false positive diagnosis of rejection in the presence of CsA toxicity. Acute CsA-induced graft dysfunction is reversible even if it persists for several days but delaying appropriate treatment of acute rejection may compromise both short and long term graft outcome. Hence caution is advised in making an empirical diagnosis of acute CsA nephrotoxicity and reducing CsA dosage unless the CsA levels are clearly in the "toxic" range (approximately > 400 ng/mL) and the clinical scenario is suggestive of this diagnosis.

The threshold for biopsy in order to more firmly establish the diagnosis varies between centers. An algorithm for approaching this common clinical problem is shown in Figure 8. One commonly followed strategy is to institute a "trial of therapy" and, if the clinical response to this is unsatisfactory, to proceed to biopsy within 48 – 96 hours. For example, if acute CsA nephrotoxicity were suspected, the CsA dose would be reduced which should lead to improvement in renal function within 24 – 48 hours, were this diagnosis correct. A presumptive diagnosis of acute rejection would mean empirical treatment with a steroid pulse. Lack of response after several days of anti-rejection treatment because of resistant rejection, CsA nephrotoxicity or another cause would be diagnosed by biopsy. The threshold for biopsy is lower in "high risk" patients: those who are highly sensitized, have previously rejected a graft or are at high risk of early recurrent primary renal disease, especially focal segmental glomerulosclerosis (FSGS) or hemolytic uremic syndrome (HUS). Biopsy results alone should not dictate management [29]; rather the constellation of clinical and histological findings should be used to shape a treatment plan. In some cases,

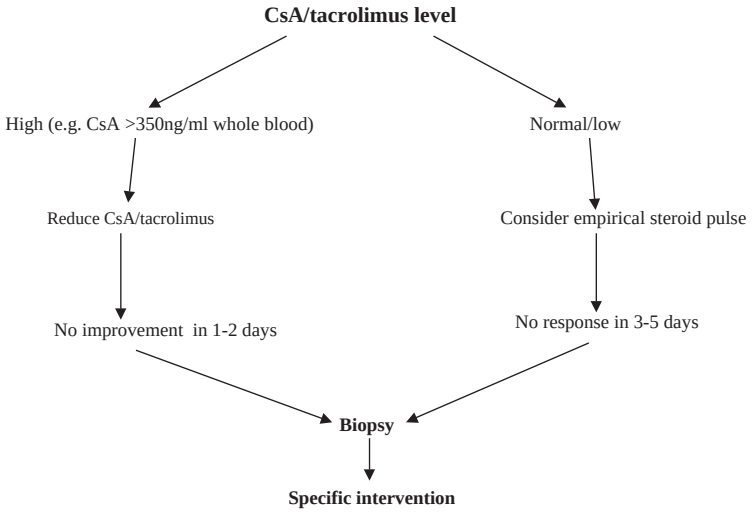

Figure 8. Algorithm for management of allograft dysfunction in early post-transplant period (prerenal and postrenal causes excluded).

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histological findings of CsA-induced damage and acute rejection may coexist.

Complications of percutaneous kidney biopsy include macroscopic hematuria (usually transient and self-limiting), transient anuria secondary to blood clots, perirenal hematoma and arteriovenous fistula. Major complications occur in < 5% of cases [56]. Graft loss is fortunately rare. There is some evidence that use of a smaller bore spring-loaded "gun" device is associated with a lower complication rate than use of the traditional Tru-Cut or Franklin-Silverman needle [66].

It has been suggested that measuring the levels of serum or urinary cytokines [70], interleukin-2 receptor (IL-2R) [27], adhesion molecules [12] or other inflammatory markers such as complement [90] and acute phase proteins [52] may be useful in diagnosing acute allograft rejection. Urinary cytology has also been advocated [28]. A sufficiently sensitive and specific serum or urinary marker might obviate the need for biopsy or aid the follow-up of treated rejection. These markers have yet to be validated in large scale multicenter human studies, however. Another concern is that infections including cytomegalovirus (CMV) could mimic acute rejection by elevating the levels of inflammatory and immunological markers. The limitations of fine needle aspiration biopsy have already been discussed. Core kidney biopsy with appropriate histology therefore remains the gold standard for diagnosing intrarenal causes of allograft dysfunction. Quantitative determination by reverse transcription-polymerase chain reaction (RT-PCR) of certain gene transcripts within renal biopsy tissue was recently shown to be a sensitive and specific marker of acute rejection [125]. Combined analysis of Fas ligand, perforin, and granzyme B gene expression yielded the most accurate results. Such specialized techniques, when proven to be highly reproducible, may assume an important role in clinical practice.

Acute Pyelonephritis

Urinary tract infections (UTIs) may occur at any time period but are most frequent shortly after transplantation because of catheterization, stenting and aggressive immunosuppression. Other risk factors are anatomical urological abnormalities and neurogenic bladder. In general, UTIs occurring in the first few months post-transplant are more severe and complicated and require more aggressive therapy than those occurring later [109]. There is evidence that acute pyelonephritis in the early post-transplant period predisposes to acute rejection. Fortunately, acute pyelonephritis and urosepsis are much less common since the widespread use of prophylactic trimethoprim-sulfamethoxazole (TMP-SMX). Fever, allograft pain and tenderness and raised peripheral blood white cell count are usually more pronounced in acute pyelonephritis than in acute rejection. Diagnosis requires urine culture but empirical antibiotic treatment is started immediately. The most commonly implicated microorganisms are gram-negative bacilli, coagulase-negative *Staphylococci* and *Enterococci* – similar to non-transplant patients [42]. Recurrent cases of pyelonephritis require investigation to rule out underlying urologic abnormalities.

Acute Allergic Interstitial Nephritis

Distinguishing acute allergic interstitial nephritis and acute rejection is difficult. Histological findings are similar and eosinophilic infiltration of the transplanted kidney may occur with either condition. Both conditions usually respond to steroids. Colvin has suggested that invasion of multiple tubules by eosinophils is strong evidence for drug induced acute allergic interstitial nephritis [26]. TMP-SMX is the drug most likely implicated in renal transplant patients.

De Novo Glomerulonephritis

De novo anti-glomerular basement membrane (GBM) disease may arise in the early post-transplant period in grafts transplanted into recipients with Alport's syndrome. Here the recipient with abnormal type IV collagen α chains produces antibodies against the previously "unseen" normal α chain in the basement membrane of the transplanted kidney. Such patients with graft dysfunction should be treated with plasma exchange and cyclophosphamide [69]. Graft failure due to anti-GBM disease in the transplanted kidney is more common in re-transplants.

Recurrence of Primary Disease

It is difficult to draw firm conclusions regarding the recurrence rate of primary kidney disease post-transplant for several reasons: the original cause of ESRD is often unknown, most relevant studies are small and retrospective with variable follow-up periods and differentiating recurrent disease from chronic allograft nephropathy is sometimes not possible. Randomized prospective trials of treatment regimens for recurrent disease do not exist. The conditions associated with recurrence in transplanted kidneys may be classified into 3 groups:

- glomerulonephritis,
- metabolic diseases such as diabetes mellitus (DM), and
- systemic diseases such as systemic lupus erythematosis (SLE) [86].

Several renal diseases may recur in the early post-transplant period. These include FSGS, anti-GBM antibody disease and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP). Tables 5a and 5b summarize the conditions which recur at any time period after transplantation. FSGS is considered in more detail below because of its relatively high frequency of recurrence and its propensity to cause severe graft injury.

Focal Segmental Glomerulosclerosis

FSGS has a reported recurrence rate of 20 – 40% [9, 127] and causes graft loss in approximately 50% of recurrent cases [9]. Risk factors for recurrence include early onset (< 15 years of age), rapidly progressive FSGS in the recipient's native kidneys and mesangial proliferation on the original biopsies. Recurrence of disease in a previous allograft puts the patient at very high risk for subsequent recurrence. Most cases present hours to weeks post-transplant. The rapidity of recurrence in some cases suggests a circulating plasma factor as the underlying etiology – there is now some experimental evidence for this [112]. Proteinuria which may be massive is the main clinical feature. Early biopsy is indicated in those at risk who develop proteinuria. Unproven treatments include plasma exchange, immunoadsorption, high dose CsA, cyclophosphamide and ACE inhibitors [69]. Those at high risk of recurrence should be offered cadaveric rather than living related kidneys.

Postrenal Dysfunction

The incidence of serious urological complications and associated morbidity in transplant recipients has decreased significantly over the last 20 years to < 10% [136]. Graft loss from urological complications is now rare. Most urological complications are secondary to technical factors at the time of transplant and manifest themselves in the early postoperative period but immunological factors may play a role in some cases.

Urine Leaks

Urine leaks usually occur in the first few weeks after transplantation and are discussed in more detail in chapter III-3. It is important to note that the clinical features may mimic those of acute rejection. An incorrect diagnosis of acute rejection and administration of steroid pulse treatment in this context may have serious consequences. Treatment in most cases involves surgical exploration and repair. Selected patients may do well with endourologic treatment [108]. Whenever urine leakage is suspected, a bladder catheter should be immediately inserted to decompress the urinary tract. The type of repair will depend on the level of the leak and the tissue viability.

Urinary Tract Obstruction

Urinary tract obstruction can cause allograft dysfunction at any time period after transplantation but is most commonly manifest in the early postoperative period. It is discussed in chapter III-3.

Table 5a. Recurrence of Metabolic or Systemic Disease after Renal Transplantation

Disease	Histological recurrence rate	Clinical recurrence rate	Time to recurrence	Treatment of recurrence	Living Related Donors	Comments
Metabolic						
Primary Oxalosis	Was high; now much improved	Was high; now much improved	Immediately onwards	Prevention is achievable goal	Yes, but cadaveric liver + kidney transplantation better	Early combined liver and kidney transplantation and intensive perioperative treatment to protect graft are best option
Diabetes Mellitus	100%	Probably most cases if prolonged survival	Approx 3 years onwards	Improved glycemic control ACE-Inhibitor	Yes	Graft loss from cardiovascular disease (death) much more important
Systemic Disease						
SLE	< 1%	Rare	–	? Cyclophosphamide	Yes	Ensure quiescent disease and serology before trasplantation
Wegener's Granulomatosis	15%	40%	From 1st week	Cyclophosphamide	Yes	Avoid transplant if disease active, ? role of monitoring ANCA
Amyloid	?	?	1 year onwards	Attempt treatment of underlying cause	Yes	Extrarenal complications determine overall prognosis; in amyloid secondary to FMF, cholchicine reduces recurence
HUS/TTP	10 – 25%	50%	Up to 5 years	Plasma exchange/ infusion	Yes, if not familial HUS	Hold transplant until > 3 months after acute disease

Abbreviations = ANCA: anti-neutrophil cytoplasmic antibodies, FMF: familial Mediterranean fever, HUS: hemolytic uremic syndrome, SLE: systemic lupus erythematosus, TTP: thrombotic thrombocytopenic purpura

Table 5b. Recurrence of Glomerulonephritis after Renal Transplantation

Disease	Histological recurrence rate	Clinical recurrence rate	Time to recurrence	Treatment of recurrence	Living Related Donors	Comments
Glomerulo-nephritis						
FSGS		40 – 50%	Hours to weeks	PE; NSAID, Steroids, ACEI	No, if risk factors present	Increased risk in children,those with rapid progression to ESRD or mesangial proliferation on biopsy
Membraneous GN	3 – 26%	50%	1 week onwards	Cytotoxics + steroids, ?ACE inhibitors	Careful consideration	High rate of de novo membraneous GN in graft; males higher risk
IgAN	25 – 60%	1 – 10%	2 months onwards	With crescents: PE, cytotoxics	Yes	Overall, graft survival is increased compared to other renal diseases
HSP	30 – 75%	Rare	Immediately onwards	?Steroids	Avoid	Avoid transplant with relapsing purpura
MPGN type I	20 – 30%	40%	–	Aspirin, steroids, cyclophosphamide	Avoid	May mimic chronic allograft nephropathy
MPGN type II	50 – 100%	10 – 20%	3 weeks onwards	?PE	No, if risk factors present	Risk factors: males, rapid progression to ESRD, nephrotic syndrome
Anti-GBM disease	5 – 10%	25%	Immediately	PE, cyclophosphamide	Yes	Hold transplant until clinical remission and negative antibodies for 6 – 12 months

Abbreviations = PE: plasma exchange, NSAID: non-steroidal anti-inflammatory drug, MPGN: membranoproliferative glomerulonephritis, FSGS: focal segmental glomerular sclerosis, IgAN: IgA nephropathy, HSP: Henoch-Schönlein purpura, Anti-GBM: anti-glomerular basement membrane, GN: Glomerulonephritis
Reproduced with permission from *Kotanko P et al.* 1997 Recurrent glomerulonephritis following renal transplantation. Transplantation *63:* 1045-1052.

Late Acute Allograft Dysfunction

The causes and evaluation of late acute allograft dysfunction are broadly similar to those of acute dysfunction. Again, prerenal and postrenal causes must be excluded. With adequate immunosuppression, acute rejection is uncommon after the first 6 months. Late acute rejection should alert the physician to prescription of inadequate immunosuppression or, more commonly, patient non-compliance [34]. Risk factors for non-compliance include younger patient age, more immunosuppression-related side effects, ethnicity (which may be a surrogate marker), lower socioeconomic status and psychological stress or illness [20, 43, 85]. Identification of at-risk patients and appropriate intervention may be helpful in limiting non-compliance. African-American patients appear to be at high risk of late acute rejection and graft loss [110]. Late acute rejection is usually treated with pulse steroids. OKT3 or ATG are less effective in reversing acute rejection that occurs more than 3 – 6 months after transplantation. The aggressiveness of anti-rejection therapy will depend on the clinical situation and biopsy findings. There is evidence that late acute rejection has a particularly deleterious effect on long-term graft outcome [73].

One group has described a series of 21 patients with asymptomatic CMV infection and late acute allograft dysfunction who did not respond to conventional anti-rejection therapy [104]. Treatment with ganciclovir resulted in stable improved renal function in 80% of cases.

Late Chronic Allograft Dysfunction

Despite major improvements in one-year graft survival since the introduction of CsA in the 1980s, chronic allograft dysfunction and allograft failure remain major clinical problems. The long-term loss rate of cadaveric kidney transplants as shown by half-life has remained quite resistant to improvements in immunosuppression but registry data from the time period 1988 – 1994 do show a modest recent increase in renal allograft half-life from 8 to 9 – 10 years [128]. Allograft failure is now one of the most common diagnoses for patients commencing dialysis. The most important cause of chronic allograft dysfunction and failure is chronic rejection/chronic allograft nephropathy. Of note, death with a functioning graft is the second most common cause of graft loss – responsible for about 40% of cases [55]. Causes of allograft loss after the first 12 months are shown in Table 6 and causes of late chronic dysfunction in Table 7.

Table 6. Causes of Allograft Loss after the First 12 Months

Cause	Percentage
Chronic allograft nephropathy	24 – 67
Patient death	22 – 48
Noncompliance	4 – 28
Recurrent disease	2 – 9
Other	2 – 13

Reproduced with permission from Bia MJ 1995 Nonimmunologic causes of late renal graft loss. Kidney Int 47: 1470 – 1480.

Table 7. Causes of Late Chronic Allograft Dysfunction

Prerenal
Transplant renal artery stenosis
Intrarenal
Chronic rejection / chronic allograft nephropathy
Chronic cyclosporine/FK506 nephrotoxicity
Recurrence of primary disease
Postrenal
Urinary tract obstruction

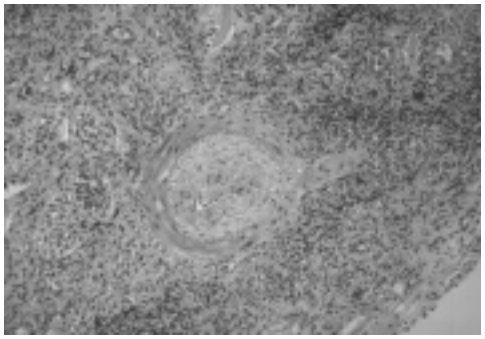

Figure 9. Chronic rejection/chronic allograft nephropathy. There is severe tubular atrophy and dropout, interstitial fibrosis and some mononuclear cell infiltration of the tubulo-interstitium. The walls of the artery are grossly thickened, predominantly due to intimal fibrosis and scattered mononuclear cell infiltration resulting here in almost complete luminal occlusion. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

Chronic Allograft Nephropathy (CAN)

This term is preferable to the older term "chronic rejection" because it encompasses the role of alloantigen-independent factors. However there is no clearcut, universal definition of what constitutes this syndrome. Clinical features are rising plasma creatinine, proteinuria and hypertension. Onset is rarely < 6 months post-transplantation. "Early" onset or other atypical features should prompt a search for another diagnosis such as recurrent disease or primary donor renal disease such as arteriosclerotic nephrosclerosis [19]. Usually there is a history of overt acute rejection episodes which may have responded poorly to anti-rejection treatment. The rate of decrease in the GFR varies widely between patients but is usually progressive and irreversible. Proteinuria is usually in the range of 1 – 2 g/day but may be massive enough to cause nephrotic syndrome. Hypertension occurs in about 90% of cases. Severe proteinuria [80] and inadequately controlled hypertension are associated with more rapid deterioration in renal function.

Chronic histological changes occur in the tubulointerstitium, large vessels and glomeruli (Figure 9). These changes are not unique to the chronic rejection process and may reflect chronic rejection, chronic CsA nephrotoxicity, hypertensive nephrosclerosis, maladaptive changes to inadequate nephron number, donor disease prior to transplantation or a combination of these processes. Distinguishing these entities on histological grounds alone is often very difficult. Fibrosis and patchy mononuclear cell infiltration of the interstitium, tubular atrophy and dropout are characteristic findings. The intima of arterial walls is thickened due to proliferation of smooth muscle and fibroblast cells and deposition of extracellular matrix material. Disruption and duplication of the internal elastic lamina may also occur. These changes (aptly termed graft atherosclerosis) result in luminal

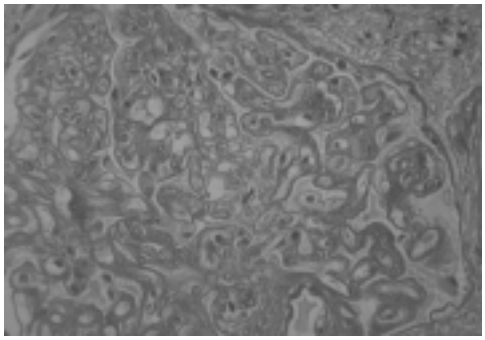

Figure 10. Chronic transplant glomerulopathy. The glomerulus is enlarged with thickening of its capillary walls and "double contouring" of its basement membranes. The latter represents damage of capillaries and regeneration of the endothelium with formation of a new basement membrane. Periglomerular fibrosis is also evident. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

Table 8. Causes of Chronic Allograft Nephropathy

Alloantigen dependent	Alloantigen independent
Acute rejection	Ischemia/reperfusion injury
Late acute rejection	Chronic cyclosporine toxicity
Poor MHC matching	Inadequate nephron number
Inadequate immunosuppression	Hypertension
	Hyperlipidemia
	? Proteinuria
	? CMV infection

narrowing or occlusion with consequent downstream ischemia. The glomeruli are frequently abnormal: collapsed and ischemic or demonstrating features of chronic transplant glomerulopathy. Chronic transplant glomerulopathy is characterized by capillary wall thickening and double-contouring, increased mesangial matrix or cells and segmental sclerosis (Figure 10). Chronic transplant glomerulopathy is often associated with severe proteinuria and is the most common cause of nephrotic syndrome in renal transplant patients. Findings suggestive of predominant CsA/FK506 toxicity are discussed below.

The pathogenesis of CAN remains incompletely understood. Alloantigen-dependent and alloantigen-independent factors are considered to be important (Table 8). Several of these factors probably interact in any given patient with CAN. Transforming growth factor-beta (TGF-β) is a cytokine produced by T cells and macrophages that has anti-inflammatory but also fibrogenic properties. Intragraft expression of TGF-β1 mRNA has been found to correlate significantly with interstitial fibrosis and chronic allograft nephropathy [118]. Interestingly, production of TGF-β is probably stimulated by both CsA and allograft injury (from rejection or ischemia). This provides an attractive hypothesis linking several of the alloantigen-dependent and -independent factors associated with the development of CAN. Figure 11 illustrates some of the postulated mechanisms through which these factors interact and lead to CAN.

Alloantigen-dependent Factors

Animal transplant models support the role of acute rejection and alloantigen dependent factors in the development of CAN. In a rat model of renal allograft rejection, reducing

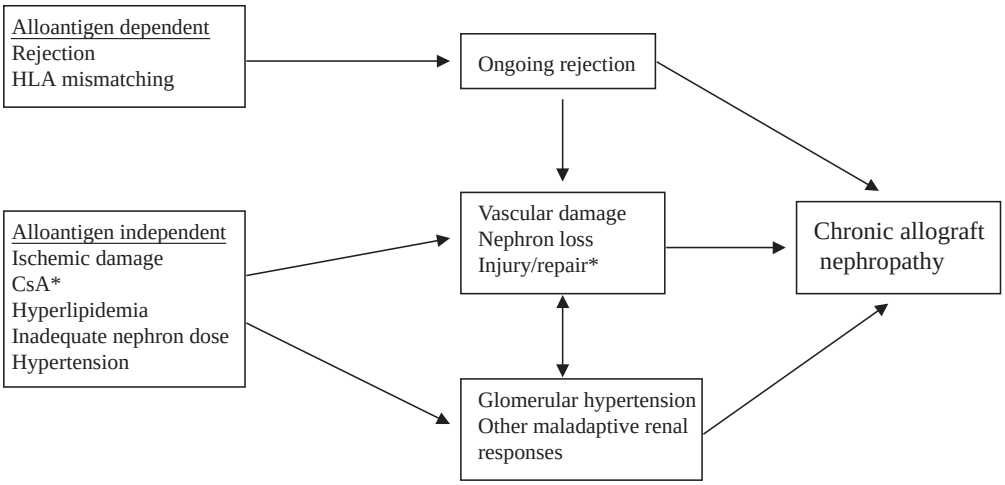

Figure 11. Simplified schematic model of the interaction between alloantigen dependent and independent mechanisms in the pathogenesis of CAN.

CsA doses increased the number of acute rejection episodes [142]. The histological changes of CAN and graft failure were directly proportional to the number of acute rejection episodes. Many retrospective human studies have shown that acute rejection episodes correlate with the later development of chronic allograft nephropathy. Multiple episodes, severe (as defined by histology or resistance to steroid pulse therapy) or late acute episodes correlate particularly strongly [79]. In addition, retrospective analyses showed that infections and CsA dosage of < 5mg/kg/day were associated with chronic rejection [5]. Infections may promote rejection by upregulation of inflammatory and immune responses. A confounding feature of CsA dosage analysis, however, is that patients with chronic renal dysfunction may have had CsA doses decreased because of fear of inappropriate immunosuppression or chronic CsA nephrotoxicity.

Further indirect support for the role of alloantigen dependent factors is the consistent finding that long-term cadaveric graft loss is associated with the degree of donor-recipient HLA mismatching [128]. Presumably loss reflects a higher incidence of chronic rejection although this has not been directly proven.

It is hoped that reduction in the incidence of acute rejection with new immunosuppressive regimens will translate into a reduction in the incidence of CAN but this has yet to be proven. MMF decreases the incidence of acute rejection in human kidney transplantation and, in animal allograft models, limits graft arteriosclerosis [93]. Long-term multicenter data with FK506 use are awaited.

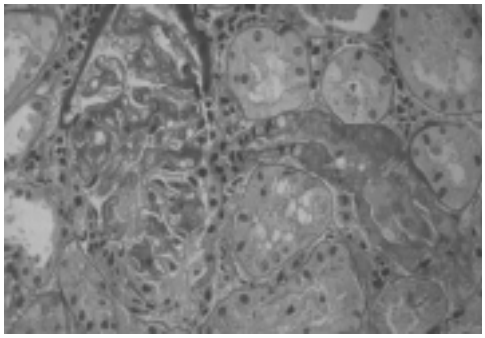

Figure 12. Chronic cyclosporine nephrotoxicity. The glomerulus shows ischemic collapse. The lumen of the arteriole is severely narrowed by the accumulation of subintimal and medial hyaline material. Many of the arteriolar smooth muscle cells have disappeared. Involvement of arterioles rather than arteries is characteristic of chronic cyclosporine nephrotoxicity. Reproduced with permission from Vella JP, Sayegh MH (In press) Diagnosis and management of allograft dysfunction. In: Brenner BM (ed): Current therapy in nephrology and hypertension; a companion to Brenner and Rector's, "The Kidney", W. B. Saunders, Philadelphia. Original photomicrograph is courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston.

Alloantigen Independent Factors

Cyclosporine

The contribution of long-term CsA therapy, particularly with currently used maintenance doses, to chronic renal allograft dysfunction remains controversial. The fact that long-term cadaveric graft survival has increased only moderately in the CsA era despite major improvements in one year survival suggests that:

- the drug's beneficial immunological effects are countered by other drug related deleterious effects on the graft such as ischemia, hypertension or production of profibrotic factors, and/or
- prevention of acute rejection episodes alone is not sufficient to prevent development of CAN [55].

Certainly, in non-renal transplant patients (e.g. those with cardiac allografts or autoimmune disease), prolonged intake of CsA is associated with significant decreases in native kidney GFR and chronic histopathologic changes on biopsy [41, 105]. The classical findings of "pure" or isolated chronic CsA toxicity are tubular atrophy with striped or focal interstitial fibrosis and arteriolar thickening and narrowing (Figure 12). There is little tubulointerstitial inflammation and arteries appear relatively normal. Glomerular ischemic collapse or sclerosis are frequent but non-specific findings. Presumably these changes are caused in part by continuous vasoconstriction induced ischemia. There is growing evidence that CsA stimulates hyperproduction of TGF-β in vivo [64, 119]. In practice, determining the independent chronic nephrotoxic effects of CsA in renal transplantation is difficult. Another confounding feature is that CsA contributes to post-transplant hypertension.

Retrospective analysis (notwithstanding the limitations inherent in such methods) suggests that long-term CsA use does not accelerate allograft dysfunction compared to non-CsA usage [96] but this is not a consistent finding [13]. Lower CsA dosage (< 5mg/kg) has been identified as a risk factor for the development of CAN [5].

Functioning Nephron Number and Hyperfiltration

An imbalance between the metabolic/excretory demands of the recipient and his/her functional renal transplant mass has been postulated to play an important causative role in the development and progression of chronic allograft nephropathy [77]. According to this theory, functioning nephron number, already limited by the presence of one rather than 2 kidneys, may be compromised further by pe-

rioperative ischemia-reperfusion injury, rejection episodes and chronic ischemia due to CsA mediated renal vasoconstriction. Progressive renal failure occurs by mechanisms presumed similar to those responsible for the continued loss of renal function in established native kidney disease. This is an important premise as interventions proven to be effective in slowing the progression of native kidney failure such as control of hypertension, reduced protein diet and ACE inhibition may have an important therapeutic role in CAN. The most likely mechanisms of progressive allograft failure involve altered renal hemodynamic responses with glomerular hypertension and hyperfiltration and "overwork" of remaining nephrons. This disease process would be exacerbated by donation of smaller kidneys (from female, old or very young donors) to larger recipients (male, large body mass). Support for this nephron dosing hypothesis comes from animal studies and retrospective analyses of human transplantation data. In a rat model of chronic renal allograft rejection, the transplantation of 2 rather than 1 kidneys prevented the development of glomerular hyperfiltration and hypertrophy and of proteinuria and glomerulosclerosis [76]. In humans, a multivariate analysis of registry data demonstrated a significant association between cadaveric graft failure and antigen-independent factors including increasing donor age, female donors and recipient body surface area (an index of body size) [23]. The impressive outcomes of living unrelated kidney transplantation further supports the nephron dosing hypothesis: a likely factor for the very high graft survival is the transplantation of a high functioning nephron 'mass' (because only healthy donors are selected and there is minimal perioperative ischemic damage). Prospective human trials to determine the role of inadequate nephron mass are not available however and 2 recent analyses have not concurred with the above findings [44, 87].

The issue of "nephron dosing" has assumed greater importance because of the pressure to use cadaveric allografts from "expanded criteria" donors. Typically these kidneys have impaired pre-transplant function because of advanced donor age (> 60 years) and/or donor disease such as chronic hypertension. Not surprisingly, short- and long-term outcomes with such grafts have generally been inferior to grafts from "normal criteria" donors [21]. Transplantation of both kidneys into one recipient would obviously double the functioning nephron number. Short-term results with dual kidney transplantation have been promising [2, 57] and further study is certainly warranted.

ACE inhibitors and probably angiotensin II (Ang II) receptor antagonists slow the rate of progression of native kidney failure by reducing systemic and glomerular hypertension and probably by additional mechanisms. Multicenter trials to study the effects of intervention with these agents in CAN are ongoing.

Proteinuria

Persistent proteinuria correlates with poorer renal survival both in native and transplant kidney disease [79]. Proteinuria may simply be a marker of renal damage but there is speculation that proteinuria per se may accelerate allograft loss from CAN. Dietary protein restriction to slow the progression of CAN has shown encouraging results in preliminary studies [39, 107] but there is concern regarding the danger of a negative protein balance in steroid-treated patients. If protein restriction is prescribed, a modest reduction in protein intake to 0.8 g/kg/day is probably safe but care should be taken to ensure plasma albumin levels remain normal. Preliminary human studies of ACE inhibitors use in CAN have shown reduction in proteinuria (see below).

Ischemia/Reperfusion Injury

Ischemia/reperfusion injury at the time of transplant is thought to be a cause of CAN because of at least 2 reasons:

– such injury amplifies the alloimmune response, predisposing to rejection mediated damage; and
– irreversible loss of functioning nephron mass from ischemic damage per se predisposes to the maladaptive responses of glomerular hypertension, nephron hypertrophy and eventual failure.

There are extensive data demonstrating that ischemic ATN (the clinical manifestation of such injury) is associated with an increased risk of late graft loss, particularly when acute rejection is superimposed [94].

Hypertension

Hypertension is one of the most common complications of renal transplantation, particularly since the introduction of CsA. It is discussed in more detail in chapter III-7. Determining the contribution of hypertensive nephrosclerosis to CAN is difficult but retrospective studies have shown that the degree of hypertension correlates with the rate of deterioration of graft function and the severity of graft histological change [17, 89]. Animal studies have shown that control of hypertension retards the progression of CAN [98]; direct clinical proof of a graft-protective effect in humans is still awaited but it is reasonable to presume that normalization of blood pressure will limit renal and extrarenal damage, as is the case with native kidney disease. The ability of ACE inhibitors to reduce glomerular hypertension and proteinuria in addition to lowering systemic blood pressure makes them attractive agents for use in many patients with CAN. Furthermore, as there is experimental evidence that Ang II stimulates renal production of the fibrogenic cytokines, platelet-derived growth factor and TGF-β [58, 59], ACE inhibition could potentially attenuate graft fibrosis. These perceived benefits of ACE inhibition in renal allograft recipients await validation in clinical practice.

CMV Infection

Infection with CMV is known to cause upregulation of MHC class I and II molecules and adhesion molecules within the renal allograft which might amplify alloimmune responses. In addition, reduction in immunosuppression during or after invasive CMV infection may predispose towards rejection. In animal models, infection with CMV enhances the development of CAN [72]. Several studies suggest an association between CMV infection and renal allograft rejection in humans [103, 104] but a direct causative link remains controversial. Poorer long-term graft survival (3 – 6% lower, irrespective of recipient CMV status) in recipients of CMV positive kidneys reflects a small but significant increased risk of death and the fact that CMV-positive are more likely than CMV-negative organs to emanate from older donors [21].

Hyperlipidemia

The prominence of the vascular lesions in CAN, the similarity of the lesions to atherosclerosis and the well-recognized role of hyperlipidemia in atherosclerosis suggest that hyperlipidemia plays a role in the pathogenesis of CAN. Hyperlipidemia is an important complication of kidney transplantation, occurring in up to 70% of patients [95]. Factors associated with the presence of post-transplant hyperlipidemia include steroids, CsA, antihypertensive drug therapy, DM and excessive weight gain. Both hypercholesterolemia [37] and hypertriglyceridemia [78] have been associated with an in-

creased risk of graft failure although some studies have not confirmed these findings. Larger prospective studies with multivariate analysis are required to firmly establish the role of lipid abnormalities in the pathogenesis of CAN as distinguishing cause and effect is difficult.

Nevertheless, as cardiovascular disease is one of the most common causes of morbidity and mortality in long-term renal allograft recipients [60], standard lipid lowering treatment is recommended for transplanted patients with other risk factors for cardiovascular disease [137]. Treatment measures include dietary modification, exercise, lipid lowering drugs and, perhaps in certain cases, alterations in immunosuppressive therapy. β-hydroxy-β-methyglutaryl-CoA (HMG-CoA) reductase inhibitors are the drug treatment of choice. There is some evidence that HMG-CoA reductase inhibitors exert an immunosuppressive effect when given with CsA [65]. Administration of pravastatin to cardiac [65] and renal [62] transplant recipients was shown to have beneficial immune-modulating effects in two small randomized prospective studies.

Diagnosis and Management of Chronic Allograft Nephropathy

The differential diagnosis of chronic allograft dysfunction is shown in Table 7. Typical clinical features of CAN are slowly rising plasma creatinine, proteinuria and hypertension. There is usually a history of one or more episodes of acute rejection. Renal ultrasound should always be performed to rule out an obstructive cause. If there is suspicion of renal artery stenosis, radiological investigation is indicated. Renal biopsy establishes the diagnosis of chronic allograft nephropathy, allows further estimation of disease severity and will occasionally yield unexpected information such as the presence of significant *acute* rejection or recurrent primary disease. In many cases however, diagnosis is assumed without histological support.

At the present time, treatment options are very limited. The potential benefit of MMF in reversing or slowing the chronic rejection process remains to be validated. If there is significant acute rejection, a single course of pulse steroid therapy should be tried. If evidence of chronic CsA nephrotoxicity predominates, cautious reduction of CsA dosage should be attempted. However, for most cases of chronic allograft nephropathy, there are no clearcut guidelines on adjusting immunosuppression. The dilemma often is: should immunosuppression be reduced to minimize its adverse effects or should it remain unchanged in an attempt to retain residual renal function for as long as possible? Hypertension should be tightly controlled with the aim of maintaining mean blood pressure < 100 mmHg (preferably nearer 90mmHg). Hyperlipidemia should also be treated in order to reduce cardiovascular morbidity and possibly slow progression of graft vascular changes. The time course to ESRD is variable but progression is rarely reversible.

As GFR deteriorates, preparations should be made for a return to dialysis. Erythropoietin (EPO), vitamin D therapy and other supportive measures may be required before dialysis resumes. Patients may elect to go back on the transplant waiting list but they should be made aware that sensitization makes allograft matching more difficult and increases the risk of rejection.

Prevention of CAN is obviously a major focus of current research. In summary, strategies that might be expected to reduce the incidence of CAN include: adequate “dosing” of functioning nephrons (including more use of living donor and dual kidney transplantation), minimizing ischemia-reperfusion injury, further reduction in the incidence of

acute rejection with the aid of improved immunosuppression, aggressive treatment of hyperlipidemia and hypertension and interruption of pathways leading to fibrosis.

Transplant Renal Artery Stenosis

Transplant renal artery stenosis is usually a late complication of transplantation. Determination of its incidence is not possible; retrospective studies report functionally significant stenosis in approximately 8% of transplanted patients [75]. Luminal narrowing of 70 – 80% is probably required to make a stenosis functionally significant. The stenosis may occur in the donor artery, recipient artery or at the anastomotic site. Causes include operative trauma or hemodynamic stress to these vessels, atheroma of the recipient vessels or faulty suture technique. Immunological factors have been postulated to play a role as case control studies have found an association with the number of acute rejection episodes [140]. Suggestive signs of functionally significant stenosis are resistant hypertension, fluctuating renal function especially with hypovolemia or ACE inhibition, edema, new bruits over the kidney and polycythemia.

Color flow doppler but not scintigraphy is a useful screening test but definitive diagnosis requires renal angiography. The initial treatment of choice is usually percutaneous transluminal angioplasty (PTA), although conservative medical management may suffice in less severe cases [111]. The clinical response rate to angioplasty is approximately 40 – 75%. Restenosis is a problem and may require repeat angioplasty or surgical repair. Surgical repair is performed when angioplasty has failed or is not possible. This is generally considered difficult and to be associated with a high frequency of graft loss but good results have been reported from some centers [106].

De Novo Renal Allograft Damage

De novo membranous glomerulonephritis has been reported to occur in up to 9% of transplanted kidneys [53]. Coexisting rejection is often present. Clinical features may be minimal or include proteinuria / nephrotic syndrome or elevated creatinine. Graft loss may occur in > 50% of cases but this high attrition rate is likely to reflect ongoing rejection [130]. Other forms of de novo glomerulonephritis causing late post-transplant dysfunction are rare. Distinguishing de novo and recurrent glomerular disease may be difficult because the cause of native kidney failure is frequently unknown.

Recurrence of Primary Disease

Cases of recurrence may be missed because failing grafts may erroneously be presumed to have CAN. Recurrent renal disease is roughly estimated to cause 2 – 4% of graft failures [86]. Intuitively one might expect that the longer the post-transplant period, the greater the risk of recurrent glomerulonephritis becoming manifest. This has proven to be the case with IgA glomerulonephritis. More information is provided in Tables 4a and 4b.

Urinary Tract Obstruction

This should always be excluded by renal ultrasound as prostatic enlargement, ureteric stones or abdominal/pelvic neoplasia may develop years after transplantation. Vesicoureteric reflux may be documented radiologically in many patients post-transplant. Reflux has been identified as a risk factor for pyelonephritis in pediatric recipients [91] but 2 recent studies have shown no adverse effects on allograft infection rate or outcome in adult recipients [38, 134].

Renal Allograft Dysfunction – Special Situations

Pregnancy

Pregnancy is generally considered safe for the mother, fetus, and renal allograft if the following criteria are met before conception: good general health for about 2 years post-transplant, stable renal function with plasma creatinine < 2mg/dL, absence of hypertension, minimal or no proteinuria, no dilation of the pelvicalyceal system on recent imaging studies and immunosuppression at maintenance doses [33]. Of course, some pregnancies occur in less optimal conditions where the risk of permanent allograft damage will be higher.

Significant renal dysfunction develops in approximately 12% of cases [33]. The main causes of renal allograft dysfunction in pregnancy are severe pre-eclampsia, acute rejection, acute pyelonephritis and recurrent glomerulonephritis. Distinguishing these causes clinically may be difficult. Pre-eclampsia and acute rejection have been reported to occur during pregnancy or within 3 months postpartum in 29% and 11% of cases, respectively [8]. Initial investigations of renal dysfunction should include plasma creatinine, creatinine clearance, 24-hour urinary protein excretion, urine culture and renal ultrasound. Acute rejection should be confirmed by allograft biopsy before instituting anti-rejection therapy. Pulse steroids are used to treat rejection. It is possible that pregnancy may affect long-term graft function by accentuating nephron hyperfiltration and overwork but this has proved difficult to assess. Meticulous monitoring of the pregnant transplant recipient is essential and should be continued for 3 months post-partum as the risk of rejection is increased during this period.

Kidney-Pancreas Transplantation

This is reviewed in chapter III-8.

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Infectious Complications in Renal Transplant Recipients

Daniel C. Brennan and Daniel Bohl

Introduction

Approximately two-thirds of renal transplant recipients will experience an infectious related complication in the first year after transplantation [1], and approximately 20% eventually will die from infection [2, 3]. These alarming rates reflect the overall or "net state" of immunosuppression associated with end-stage renal disease (ESRD) and transplantation [4] as well as donor and environmental exposures. In addition, the robustness of a recipient's immune system depends on several factors including age, nutrition, and comorbid conditions. The age of patients wait-listed for transplant is increasing [5], and many candidates are diabetic and malnourished from ESRD. Both uremia and the dialysis procedure itself are immunosuppressive [6]. Furthermore, many patients receive immunosuppressive therapy as treatment for their renal disease prior to receiving a renal transplant. Thus, the immunosuppressed state begins pre-transplantation. The donor may transmit immunomodulatory infectious agents such as cytomegalovirus (CMV) and hepatitis C virus (HCV), which can cause disease and predispose to other opportunistic infections. The intensity of the immunosuppressive regimen contributes significantly to the net state of immunosuppression. Finally, all individuals are exposed constantly to infection in the community and increasingly more resistant organisms in the hospital environment. Whether an individual develops signs and symptoms of an infectious process depends on the net state of immunosuppression and the appropriate use of preemptive, prophylactic and treatment strategies.

Pre-transplant Evaluation

As with any medical evaluation, the pre-transplant evaluation begins with a detailed history and physical examination. The goal is to assess for conditions or exposures that may predispose the candidate to future complications, particularly infections, which require treatment or prophylaxis. The surgical evaluation focuses on prior surgeries, the presence of atherosclerotic disease, and obesity that may predict poor wound healing and a predisposition to infection. The medical evaluation is a comprehensive overview to uncover past exposures including childhood illnesses with attention to viral infections and mononucleosis, endemic infections like coccidioidomycosis or histoplasmosis, and sexually transmitted infections such as gonorrhea, chlamydia, HIV, HPV, syphilis, and herpes. Occupational and pet exposures as well as consumption of well water are also queried. The medical history also includes an extensive review of systems to determine the presence of any active infectious disease or pre-

Table 1. Pre-transplant screening.

Serologies:
– Cytomegalovirus
– Epstein-Barr virus
– Varicella-zoster virus
– Herpes simplex 1 and 2 viruses
– Hepatitis A, B and C viruses
– Human immunodeficiency virus
– Rapid plasma reagin
– Endemic fungi
Tuberculin skin test
Urinalysis with culture
Pelvic or prostate exam
Chest radiogram
Dental evaluation
Tests to consider
– Toxoplasma serology
– Human T-cell leukemia virus
– Gallbladder ultrasound
– Stool culture
– Stool ova and parasite

disposing risk factors. These include a history of dental caries, sinusitis, chronic obstructive pulmonary disease (COPD), tuberculosis (TB) or a positive purified protein derivative (PPD), valvular heart disease, diverticulosis, hepatitis, urinary tract infections (UTI), prostatitis, diabetes mellitus (DM), blood transfusions, and alcohol or drug abuse. Pre-transplant screening studies for occult and latent infections are listed in Table 1, and appropriate evaluation and treatment of positive studies are necessary prior to transplantation.

Special attention is given to the underlying renal disease and its treatment. Patients on immunosuppressive medications as treatment for their primary renal disease will be predisposed to infectious complications and recurrence of their disease post-transplantation. Pre-transplant nephrectomy may be necessary for infected nephrolithiasis, polycystic kidney disease, or reflux nephropathy [7]. Renal replacement therapy with peritoneal dialysis (PD) prior to transplant may be at an increased risk for post-operative infectious complications compared to hemodialysis (HD) [8]. The PD catheter can be removed after evidence of graft function to prevent infection [9, 10]. The integrity of the hemodialysis (HD) access should also be assessed. Tunneled and peripherally inserted dialysis catheters pose an increased risk for skin- and water-borne infections. Polytetrafluoroethylene (PTFE) grafts are also more prone to infection than native arteriovenous fistulas. Screening for occult non-functioning graft infections should be considered in patients with a history of frequent bacteremia or fever of unknown origin [11].

An immunization history is obtained and pre-transplant vaccinations should include tetanus, diphtheria, inactivated polio [12], influenza [13], pneumococcus [14], hepatitis B [15], hepatitis A [16] and *Haemophilus influenzae* type B [17]. The recently developed conjugate pneumococcal vaccine appears equivalent to the polysaccharide vaccine [18]. Live vaccines for measles and varicella should be given several months prior to transplantation. The varicella vaccine is safe and effective in pediatric transplant patients [19] and should be considered for adults without a history of chickenpox or who have a negative varicella-zoster virus (VZV) titer.

Donor-related Infectious Disease

All donors require screening for human immunodeficiency virus (HIV) 1 and 2, human T-cell leukemia (HTLV), hepatitis A, B, and C, CMV, Epstein-Barr virus (EBV), herpes simplex virus (HSV), VZV, syphilis, and Toxoplasma gondii which can be transmitted from donor to recipient. Donors should have

Table 2. Human herpesviruses and associated diseases.

Virus	Disease
HHV-1: Herpes simplex 1 (HSV-1)	Herpes labialis
HHV-2: Herpes simplex 2 (HSV-2)	Herpes genitalis
HHV-3: Varicella-zoster virus (VZV)	Chicken pox, shingles
HHV-4: Epstein-Barr virus	Mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, posttransplant lymphoproliferative disorder (PTLD), oral hairy leukoplakia
HHV-5: Cytomegalovirus (CMV)	Cytomegalovirus disease, salivary gland virus disease
HHV-6: Human herpesvirus 6	Roseola subitum
HHV-7: Human herpesvirus 7	Roseola subitum, pityriasis rosea
HHV-8: Human herpesvirus 8	Kaposi's sarcoma, effusion lymphoma, multifocal Castleman's disease

screening urinalysis and urine cultures. Cadaveric donors should have screening blood cultures especially when there has been a prolonged hospitalization prior to donation.

Viral infections transmitted from donor to recipient may lead to significant morbidity and mortality. They may cause primary infection, disseminated disease, and viral associated cancer such as post-transplantation lymphoproliferative disease (PTLD) from EBV or Kaposi's sarcoma from human herpes virus (HHV) 8. HIV remains a contraindication to organ donation. Similarly, donor seropositivity for hepatitis B virus (HBV) as evidenced by hepatitis B surface antigen (HBsAg) positivity is a contraindication to organ donation. However, the risk of transmission of HBV to kidney recipients from donors with evidence of prior HBV infection with core antibody positive but surface antigen negative (HBcAb+, HBsAg–) is low and is only a relative contraindication to transplantation [20, 21]. Transplantation of HCV donor seropositive (D+) kidneys into recipients who are HCV seronegative (R–) has been associated with post-transplant liver disease and increased mortality and is generally avoided. Transplantation of HCV D+ into recipients who are seropositive (R+) is controversial but does not appear to effect short-term graft survival or mortality [22, 23]. In general, donor seropositivity for HSV, VZV, EBV, HHV 8, or CMV is not a contraindication to donation even when the recipient is seronegative.

Bacterial contamination of cadaveric kidneys may be as high as 25% but generally is not a contraindication to transplantation [24]. Cadaveric donors typically receive a cephalosporin antibiotic during the procurement operation and recipients often receive perioperative antibiotic prophylaxis [25]. Systemic bacterial infection of a donor is considered a contraindication to transplantation but has been performed successfully [26, 27]. Other infections such as syphilis, TB, fungal and other viral infections should be evaluated on a case-by-case basis.

Table 3. Timetable of infections after renal transplantation.

Time after transplantation	Infection
0 – 1 month	Wound infections Line sepsis Urinary tract infections Pneumonia Herpesviruses Oral Candidiasis
1 – 6 months	Polyomavirus Cytomegalovirus Pneumocystis carinii Aspergillus fumigatus Candida species Nocardia species Toxoplasma gondii Listeria monocytogenes Hepatitis B and C Histoplasmosis Coccidioidomycosis
Beyond 6 months	Community infections Cytomegalovirus retinitis Cryptococcus Polyomavirus Mycobacteria

Table 4. Prophylaxis in transplant patients.

Infection	Prophylaxis
Wound infections	Perioperative antibiotics
Oral candidiasis	Clotrimazole or nystatin
Cytomegalovirus	Ganciclovir or valganciclovir
Herpes simplex viruses	Acyclovir
Pneumocystis carinii	TMP-SMX*, dapsone, pentamidine
Urinary tract infections	TMP-SMX, ciprofloxacin
Varicella zoster virus	Zoster immuno-globulin, acyclovir

*Trimethoprim-sulfamethoxazole

Timing of Post-transplant Infections

Infections occurring post-transplant can be divided into three time frames: the first month, the second through sixth month, and beyond six months (Table 3). Recipients are susceptible to certain infections in each period because of the different levels of immunosuppression and environmental exposures. However, some infectious agents may shift out of their typical time frame with a change in antirejection medications or preemptive and prophylactic antibiotics (Table 4).

The infectious risk during the first month is primarily nosocomial and related to untreated infections in the donor or recipient, the surgical procedure, and the initial hospitalization. The donor and recipient have been screened for infection prior to transplantation, and cultures are taken at the time of the surgery. With immunosuppression, occult infections may present and should be dealt with promptly. Perioperative antibiotics rarely have been shown to reduce transmitted bacterial infection but often are given to treat possible bacterial contamination [25, 28]. Reduction in post-surgical risk of infection relies on the technical skill of the surgical team and early removal of foreign bodies such as endotracheal tubes, vascular access lines, drainage tubes and catheters. Reverse isolation or the use of gowns, gloves, and masks for those having contact with the patient is also not warranted even when the patient is neutropenic [29]. Many programs forbid live plants

on the transplant floor or do not allow any uncooked food to be served to renal transplant patients. However, simple commonsense measures such as food washing and good hand washing are probably all that is necessary.

The classical mnemonic (the five W's) for evaluation of fever in any surgical patient: wind, wound, water, walking, wonder drugs, is germane for the kidney transplant recipient. These patients are at risk for conventional bacterial pneumonia from atelectasis; bacterial and candidal wound infection – particularly when fat necrosis occurs or when hematomas, seromas, urinomas, or lymphoceles are present; and UTIs associated with indwelling urinary catheters. Good pulmonary toilet and early ambulation reduce the risk of pneumonia. The prophylactic use of double strength trimethoprim/sulfamethoxazole (TMP-SMX 320 mg/1,600 mg) orally (PO) regardless of the serum creatinine while the bladder catheter remains in place has reduced the risk of bacterial UTI to < 10% and the risk of blood stream infections by 10-fold [30]. The optimal duration and dose of continued prophylaxis are unknown. Because of its protection against multiple opportunistic infections (see below) we continue TMP-SMX prophylaxis for life in non-allergic patients, although many centers only continue such prophylactic therapy for the first post-transplant year.

HSV 1 and 2 and HHV 6 may be reactivated in the first month. Less commonly VZV, EBV, and CMV in the recipient also may reactivate early. New or primary viral infection from the donor generally does not become symptomatic until after the first month. Low-dose acyclovir 200 – 400 mg PO twice daily is effective prophylaxis against reactivation of HSV 1 and 2 [31]. Although high-dose acyclovir (800 mg PO 4 – 5 times/day) was reported to be effective for prevention of CMV [32], subsequent studies have shown that high-dose acyclovir has little role for prevention of CMV [33, 34, 35]. In contrast, oral ganciclovir is highly effective for preventing most herpes virus infections including HSV 1 and 2, VZV, EBV, CMV, and possibly HHV 6 but not HHV 7 [36, 37, 38, 39].

The second to the sixth month post-transplantation is the period when transplant related opportunistic infections are most likely to arise. These infections include CMV, *Pneumocystis carinii, Aspergillus fumigatus, Candida* species, *Nocardia* species, *Toxoplasma gondii*, and *Listeria monocytogenes*. Reactivation of quiescent donor and recipient infections also occur such as CMV, HBV, HCV, HHV 8, polyoma virus (BK), mycobacterium, histoplasmosis, and coccidioidomycosis.

By six months most transplant programs have significantly tapered immunosuppression to a relatively low basal state, and the profound immunosuppressive effects of anti-lymphocyte induction therapy have resolved as well. Thus, historically after 6 months most patients suffer from the same infections seen in the general community including recurrent cold sores, influenza, UTIs, diarrhea, and pneumococcal pneumonia. There are a few exceptions to this general rule. CMV retinitis tends to occur late and may occur contemporaneously with reactivation of other herpes infections including EBV, HSV, and VZV [40, 41]. The presence of herpes or zosteriform lesions may be sentinel lesions for CMV [40]. Another exception to this general rule is that some patients develop acquired immunoglobulin deficiencies post-transplantation. These may develop from immunosuppression, CMV infection or vitamin B_{12} deficiency and especially predispose the patients to recurrent infections with encapsulated organisms [42]. Finally, the time course of infections described above reflects the state of

transplantation from approximately 1985 to 1995.

Beyond six months, transplant recipients may be still at risk from infections traditionally seen the middle period. The use of newer, more potent immunosuppressive agents such as tacrolimus and mycophenolate mofetil (MMF) are being used more frequently not only to maintain immunosuppression but also to replace induction therapy with antilymphocyte agents. Thus, the recovery of the immune system from the antilymphocyte agents over the first 3 – 6 months does not occur. Instead, it may be replaced by a continuous and prolonged increase in the net state of immunosuppression from the combination and higher levels of these immunosuppressive medications. Initially, tacrolimus appeared to increase MMF levels [43], but in actuality, cyclosporine decreases MMF levels [44]. Thus, the combination of tacrolimus and MMF is more immunosuppressive. Also, the maintenance dose of MMF has been 2 – 3 g/d, but it now appears that only 500 mg b.i.d. is the safest dose [45]. Finally, episodes of acute rejection and chronic rejection are treated by increasing the net state of immunosuppression further predisposing patients to opportunistic infections.

Evaluation of Fever in the Renal Transplant Recipient

The presence of fever in the transplant recipient may represent a broad range of conditions including infection and rejection. Fever early after transplantation suggests rejection rather than infection [46] and is associated with an acute decline in kidney function and graft tenderness. On the other hand, the presenting signs and symptoms of infection may be unusual because of the use of immunosuppression. An aggressive approach to diagnosis is appropriate because of the differences in treatment and potential morbidity. Cultures of urine and blood and a chest radiograph (CXR) are obtained. A buffy coat specimen is sent for detection of CMV by polymerase chain reaction (PCR) for those patients at risk. Clues from the history, physical, and environmental exposures help direct the investigation. Empirical broad-spectrum antimicrobial therapy is initiated early, prior to the determination of a specific etiology. A more aggressive evaluation is pursued when there is an inadequate response to treatment or failure to identify an etiologic agent. The likelihood of PCP is low in patients without a recent history of CMV or in patients compliant with TMP-SMX prophylaxis; so bronchoscopy with lavage and biopsy are not usually necessary.

For outpatient therapy, ciprofloxacin 500 mg or levofloxacin 250 mg PO/day is initiated. This dose is used since the glomerular filtration rate (GFR) for most transplant patients does not exceed 50 ml/min. Alternatively, oral azithromycin 500 mg PO on Day 1 followed by 250 mg PO daily for four days is initiated. Ciprofloxacin has mild effects on cyclosporine and tacrolimus metabolism that can usually be monitored. Achilles tendonitis and tendon ruptures have been reported in renal transplant patients taking quinolone antibiotics. Although azithromycin is a macrolide antibiotic, it does not inhibit the cytochrome P450 IIIa enzyme system and does not increase cyclosporine and tacrolimus levels like other macrolide antibiotics such as erythromycin and clarithromycin. For patients who require hospitalization, we typically use vancomycin and ceftazadime or cefepime for the first 48 – 72 hours pending the identification of a specific infectious agent.

Bacterial Infections

Over 50% of renal transplant recipients will experience a bacterial infection within the first year [1, 47]. The major sites of infection include the urinary tract, blood stream, and lungs. Urinary tract infections (UTIs) are the most common bacterial infections post-transplantation with an incidence varying from 35 – 79% [48]. Typical pathogens include *Klebsiella, E. coli, Proteus, Enterococci, Enterobacter, Staphylococci, Pseudomonas*, and rarely *Corynebacterium*. Recurrent infections should be investigated with ultrasound or computed tomography to rule out abscess or other nidi of infection. Prophylaxis with TMP-SMX or ciprofloxacin reduces the incidence of UTIs dramatically. Sepsis occurs in less than 5% of recipients per year but is the leading cause of death from bacterial infection in renal transplant recipients [3, 49]. The most likely sources are urinary, pulmonary, and gastrointestinal, and the most common organisms are Gram-negative bacilli. As reported recently, pneumonia occurred with an incidence of 2.86 episodes per 100 patient-years in the United States, or rather 4.7% of renal transplant recipients received a primary diagnosis of pneumonia over an average of 1.65 years [50]. This incidence is similar to prior reports in which there was a mortality rate ranging from 12.5 – 40% [3, 51, 52]. The infectious agent in the majority of patients is never determined. This is likely because of the low yield of blood and sputum cultures, and clinical responds to antibacterial therapy. However, in patients who undergo bronchoscopy, fungal and viral etiologies including *Pneumocystis carinii* and CMV account for nearly half of organisms isolated [52, 53]. In patients who are hypoxic on presentation or do not respond to initial therapy, an invasive approach is warranted because of the concern for a non-bacterial etiology.

Legionellosis

Legionella pneumophila is the most common *Legionella* species causing infection in renal transplant recipients. It usually presents as pneumonia with a peripheral patchy infiltrate on CXR that may progress to consolidation. *Legionella* is frequently associated with epidemics and has been linked to drinking water, contaminated respiratory equipment, heating and air conditioning ventilation systems. In patients hospitalized with pneumonia at risk for legionellosis, the first tests are a urine *Legionella* antigen and culture with selective media. Diagnosis of *L. pneumophila* serogroup 1 can be made by detection of urine antigen. Positive blood or sputum culture diagnosis of legionellosis is infrequent because of its slow growth and special media requirements. Alternatively, acute and convalescent serologic studies may be obtained, although empirical therapy has usually been initiated long before the diagnosis is made in this manner. Direct fluorescent antibody (DFA) testing of sputum or bronchoalveolar lavage specimens is rapid and specific but technically difficult [54]. PCR has been used to detect *Legionella* and when commercially available likely will be a rapid and useful test.

Empirical treatment of community-acquired pneumonia includes a macrolide or a fluoroquinolone. Both agents have activity against *Legionella*. Erythromycin is the classic treatment, but erythromycin drastically increases cyclosporine and tacrolimus levels through inhibition of the cytochrome P450 IIIa system. Azithromycin, which is also a macrolide antibiotic or a fluoroquinolone including ciprofloxacin are the preferred medications. Doxycycline is an acceptable alternative. Rifampin also has activity against *Legionella* but increases cytochrome P450 activity and drastically reduces cyclosporine and tacrolimus levels. TMP-SMX used for

PCP prophylaxis may also be effective prophylaxis for *Legionella* [55].

Nocardiosis

Nocardia infections are most commonly caused by *Nocardia asteroides*. The infection typically begins in the lungs and then may disseminate in up to 50% of patients usually to the central nervous system (CNS) or subcutaneous tissue. The most common presentation is pulmonary nodules on CXR that may cavitate or form abscesses. CNS involvement is common and all patients with a diagnosis of *Nocardia* require that CNS involvement be excluded [56]. Less commonly skin involvement occurs with the presence of "sulfur" granules. Diagnosis is presumptive with the find of long, narrow, branching, acid fast, Gram-positive filaments on Gram stain and confirmed with culture. The treatment of choice is sulfonamides or TMP-SMX although a variety of other agents including minocycline, ampicillin, ciprofloxacin, and ceftriaxone may be effective. To prevent relapse, a long duration of therapy is necessary with recommendations that vary up to one year. TMP-SMX used for PCP prophylaxis also may be effective prophylaxis for *Nocardia*.

Listeriosis

Listeria monocytogenes is found naturally in soil and water and may contaminate raw foods including dairy products, vegetables, and meats. Infections historically have been most common during the first two months post-transplantation and most commonly during the months of July – October. The portal of entry is the gastrointestinal tract and patients may present with gastroenteritis. The majority of patients are febrile although only 1/3 will have bacteremia. Unfortunately, 2/3 of renal transplant patients present with CNS infection, and listerial meningitis are associated with a 1/3 fatality rate [57]. Examination of the cerebrospinal fluid (CSF) shows a predominance of polymorphonuclear monocytes with a relatively low glucose content and Gram-positive bacilli. The absence of bacteria in the CSF is actually more common and the exam should be repeated in 1 – 2 days. Intravenous (IV) ampicillin is the treatment of choice. TMP-SMX is effective for treatment and when used for PCP prophylaxis may also be effective prophylaxis.

Salmonellosis

Non-typhoid *Salmonella* infection in renal transplant patients is 20 times more common than in the non-immunocompromised adult [58]. The most common presentation is a febrile illness with bacteremia. However, *Salmonella* infection may occur at multiple sites from septic metastasis and recurrence is common. Suggestive symptoms or recurrence requires investigation to find a source such as endocarditis, arteritis, gallstones, or an infected dialysis graft. Because of the high mortality rate of 15 – 20%, concern for endovascular infection, and increasing antibiotic resistance, initial therapy for serious infections should include both a third-generation cephalosporin and a fluoroquinolone [59]. TMP-SMX used for PCP prophylaxis may also be effective prophylaxis for *Salmonella*.

Helicobacter pylori

Helicobacter pylori (Hp) is a major cause of gastritis and gastroduodenal ulceration. The prevalence of Hp in renal transplant recipients varies from about 30 – 60%. Hp de-

tected on biopsy and with antibody assays has been variably associated with dyspepsia. However, Hp is associated with mucosal-associated lymphoid tissue (MALT), which is a form of post-transplant lymphoproliferative disease (PTLD) [60]. If MALT with positive Hp is diagnosed, the patient should undergo eradication of Hp and remain on prophylaxis to prevent relapse [61]. Hp antibody is not an absolute marker since seropositive patients have sero-reverted after transplantation.

Ehrlichiosis

Ehrlichia cause two distinct but clinically similar diseases. Human monocytic ehrlichiosis (HMG) caused by *E. chaffeensis* and human granulocytic ehrlichiosis (HGE) caused by a yet undetermined species of *Ehrlichia*. Both forms have been reported in renal transplant recipients [62, 63]. HGE occurs in the northeastern and midwestern states, while HME occurs in the south central and southeastern states. Both diseases are transmitted by ticks and occur predominately in the spring and summer months. Patients present with an abrupt onset of non-specific signs including fever, chills, headache, myalgias, arthralgias, and malaise usually 1 – 2 weeks after a tick bite. A rash and CNS manifestations are more common in HME. Laboratory data shows leukopenia, thrombocytopenia, elevated transaminases, and occasionally anemia. Diagnosis can be made based on the presence of morulae on peripheral blood smear, PCR, and indirect immunofluorescence serology. Treatment consists of a 2-week course of doxycycline. Longer courses may be necessary if the concern for co-infection with other tick-borne illnesses exists. Rifampin is an alternative treatment.

Viral Infections

Infections with the herpesvirus group followed by hepatitic infections are the most common and most concerning viral infections encountered in renal transplantation. Other viruses of concern include adenoviruses, respiratory syncitial viruses, influenza virus, and polyomaviruses.

Herpesvirus Infections

There are currently eight human herpesviruses (HHV) identified. All are fairly ubiquitous and characterized by development of a latent state that may be reactivated with stress or immunosuppression.

Herpes Simplex Virus

Human simplex virus (HSV) occurs as types 1 and 2. Type 1 is commonly associated with herpes labialis and type 2 is more often associated with herpes genitalis. However, both types may be cultured from either location. Approximately 2/3 of adults have evidence of prior infection with HSV. After acute infection the virus remains latent in the sensory nerve ganglia. Reactivation may occur within the first month after transplantation and most commonly presents as mild ulcer-like mucocutaneous lesions but may cause zosteriform lesions or other skin lesions. HSV esophagitis may cause dysphagia and mimic candidiasis. Less commonly HSV can cause pneumonitis, hepatitis, encephalitis, nephritis, and rarely disseminated disease. Diagnosis is made by demonstration of multinucleated giant cells on a Tzanck test,

culture, PCR for HSV DNA, or DFA. PCR for HSV DNA in the CSF is the preferred test for CNS infection. A diagnostic increase in IgG or IgM serology may also be helpful. HSV contains a thymidine kinase that readily phosphorylates acyclovir to make this virus the most sensitive of the herpes to acyclovir. The standard therapy for mucocutaneous lesions is acyclovir 200 mg PO 4 – 5 times/day. Valacyclovir and famciclovir are alternatives with less frequent dosing schedules. More serious cases may require treatment with IV acyclovir 5 – 15 mg/kg every 8 hours. Patients who do not respond to treatment after 1 week or who develop new lesions while on therapy require the virus be isolated with antibiotic susceptibilities. Immunosuppressed patients are about 10 times more likely to have resistant HSV that requires treatment with foscarnet or cidofovir [64]. Because HSV lesions may indicate contemporaneous CMV or EBV reactivation, these infections should be ruled out [40, 41]. Low-dose acyclovir 200 – 400 mg PO twice to three times daily is effective prophylaxis for HSV. In studies for CMV prophylaxis, valacyclovir and ganciclovir are effective for HSV prophylaxis as well [37, 65]. However, once prophylaxis is discontinued, patients may develop HSV infections.

Varicella-Zoster Virus

Approximately 90% of adults have prior evidence of infection with VZV. Reactivation causes shingles or zoster in a dermatomal distribution. However, dermatomal pain without cutaneous manifestations occurs. The appearance of dermatomal vesicular lesions is usually enough to make the diagnosis and it can be confirmed with the finding of multinucleated giant cells on Tzanck smear, PCR and DFA. The cutaneous lesions may act as a portal of entry for secondary bacterial or fungal infections. Primary infection in the remaining 10% may present as skin lesions, pneumonia, encephalitis, pancreatitis, hepatitis, or disseminated intravascular coagulation and has a high mortality rate.

Treatment for zoster is a 7-day course of either acyclovir 800 mg PO 5 times/day, famciclovir 500 mg PO 3 times daily, or valacyclovir 1,000 mg PO 3 times daily. For primary VZV infection, acyclovir 10 mg/kg every eight hours for seven days is administered as well as varicella-zoster immunoglobulin (ZIG). For seronegative patients with exposure to chicken pox or VZV, ZIG should be administered within 72 hours and acyclovir 200 mg PO five times/day begun. Low-dose acyclovir or ganciclovir use for prophylaxis of HSV or CMV is probably effective prophylaxis for VZV reactivation as well. Seronegative patients should receive vaccination prior to transplantation since the vaccine is contraindicated after transplantation. However, the vaccine has been demonstrated to be safe in pediatric transplant patients despite concerns for the use of live vaccines in solid-organ transplant recipients. A minority of patients will develop post-herpetic neuralgia (PNH), although immunosuppression is not a risk factor [66]. Multiple agents include gabapentin, tricyclic antidepressants such as amitriptyline, oxycodone, and topical capsaicin are effective for reducing symptoms [67].

Epstein-Barr Virus

Approximately 95% of the adult population has serologic evidence of previous infection with EBV, and the majority of seronegative recipients seroconvert within the first year after transplantation. EBV may cause a mono-

nucleosis-like syndrome, chronic fatigue, or fever of unknown origin (FUO), but has also been associated with Burkitt's lymphoma, nasopharyngeal carcinoma and in transplant recipients, PTLD. EBV has the innate ability to transform and immortalize B cells. An extrachromosomal EBV particle is evident in the nucleus of transformed B cells. In immunocompetent individuals, a latent carrier state exists because proliferation is contained by cell-mediated immunity. In transplant recipients, cell-mediated immunity is impaired and patients are prone to uncontrolled proliferation resulting in PTLD. These altered lymphoid cells are usually of recipient origin but can be donor derived [68]. It can have a broad range of presentations from plasma cell hypertrophy to malignant lymphoma. It can be local or extensive and nodal or extra-nodal. Risk factors for the development of PTLD include EBV seronegativity, OKT3, tacrolimus, and CMV sero-mismatch. PTLD occurs in 1 – 2% of patients, typically occurs within the first year, and has a high mortality rate. PTLD that occurs within the first year is often polymorphic, EBV positive, and more responsive to reduced immunosuppression. Late PTLD is often monomorphic and EBV negative, and it requires more aggressive treatment. This dichotomy suggests different pathogeneses.

EBV is susceptible to both acyclovir and ganciclovir. Because EBV and CMV are reactivated contemporaneously and acyclovir has little activity against CMV, ganciclovir is the drug of choice for those patients with EBV who are at risk for CMV. It is important to realize that PTLD is not an infectious disease per se. Nevertheless, acyclovir and ganciclovir have been used to treat PTLD. The initial treatment is reduction in immunosuppression. For limited disease surgery and radiation are treatment options, and for extensive or refractory disease, therapies including -interferon, rituximab, and cytotoxic regimens have been used with variable success [69]. Prophylaxis of CMV with ganciclovir may reduce the risk of PTLD.

Cytomegalovirus

Cytomegalovirus (CMV) is the most important infectious agent affecting renal transplant recipients and is a significant cause of increased morbidity and mortality in this population. CMV infection occurs in up to 80% of all renal transplant recipients [70] while disease occurs in only 8 – 32% [71]. The wide range in the incidence of infection and disease results from varying intensities of immunosuppression used and the frequency and methods used to monitor CMV infection. Infections can occur as primary infections in a seronegative patient or as reactivation of a latent virus or re-infection in a seropositive patient. New infections can be acquired from the community, CMV positive blood products, or a CMV positive donor kidney. Infection may progress to disease with a wide variety of end organ involvement. Symptomatic disease can present as a CMV syndrome of fever, leukopenia, thrombocytopenia, and elevated liver enzymes. Severe disease can involve the lungs, liver, gastrointestinal tract, pancreas, kidneys, lower urinary tract, heart, eyes, and skin. CMV has been implicated as a cause of acute and chronic graft dysfunction as well as long-term graft loss. CMV has been associated with atherosclerosis including coronary artery restenosis and renal artery stenosis. Finally, CMV is able to suppress the immune response and predisposes to co-infections with other viruses, bacteria, and fungi. Risk factors for CMV disease include antilymphocyte therapy for induction or rejection treatment, active infection with other herpes-

viruses, high-dose steroids, high-dose mycophenylate mofetil, and CMV sero-mismatch.

The incidence and severity of CMV disease has been associated with the CMV serostatus of the kidney donor and recipient. Concern has mainly focused on avoiding CMV infection in the CMV D+/R– group because this group has historically been at greatest risk for severe primary infection during the first three months post-transplant. CMV infections occur in 70 – 95% of D+/R– patients and symptomatic disease occurs in 40 – 60% [70, 71, 72]. However, analyses of data from the United States Renal Data System (USRDS) and United Network of Organ Sharing (UNOS) between 1989 and 1994 revealed that by three years, it is the D+/R+ group and not the D+/R– group that has the worst graft and patient survival [73]. The reason for this is not entirely clear but may reflect the prevalence of multiple CMV virotypes and that the D+/R+ patients have a double CMV exposure. Also, although the incidence of infection is similar between D+/R– and D+/R+, the D+/R+ patients only experience about half the number of symptomatic infections. Therefore, D+/R+ patients likely are exposed to prolonged and untreated subclinical CMV effects. However, a more recent evaluation from 1995 – 1997 [74] shows that it is the D+/R– group that has the worse graft survival. Whether this changes is from better surveillance and treatment or widespread use of prophylactic strategies again is not understood.

Rapid and accurate diagnosis of CMV is important because of its increased morbidity. Until recently, the available techniques for diagnosis of CMV were limited to histological identification of CMV inclusion bodies, and viral culture. These techniques are labor intensive, not completely sensitive, and the time from primary infection or reactivation to detection of CMV is protracted, allowing for undetected and untreated disease progression. Serology is not useful for diagnosis of an acute infection. An IgM seroconversion typically takes 16 weeks to develop and an IgG response may take an additional 2 – 3 weeks for conversion [75]. Additionally, transplant recipients may fail to produce an antibody response despite other evidence for viremia [76]. Newer techniques include shell vial, pp65 antigenemia, and nucleic acid detection assays including PCR of RNA and DNA, hybrid capture assay, branched DNA assay, and nucleic acid sequence-based amplification. In addition to a rapid result, these assays provide a quantitative measure of viral burden that allows for diagnosis, therapeutic monitoring, and assessment of new medications and treatment protocols. The most appropriate test for diagnosis of CMV is an evolving issue and varies based on availability and cost. DNA PCR and the hybrid capture assay are both rapid, quantitative assays that can be performed on stored samples and higher viral loads are associated with CMV disease [77].

Multiple strategies have been used to reduce the morbidity and mortality of CMV infection and its associated costs. Avoiding CMV sero-mismatching through organ allocation is not feasible or worthwhile [73]. During CMV disease, MMF or azathioprine doses should be reduced or discontinued. Therapeutic treatment of established CMV disease is primarily with the antiviral agent ganciclovir given intravenously. There is accumulating data that valganciclovir, which is approved for prophylaxis of CMV may also be effective for treatment and may be given orally. Although CMV-infected cells lack a thymidine kinase necessary to phosphorylate acyclovir, they do contain a phosphokinase which is a product of the CMV UL 98 that is capable of phosphorylating ganciclovir into an active moiety. Typical treatment is

ganciclovir 5 mg/kg IV every 12 hours or valganciclovir 900 mg orally twice daily for 2 – 3 weeks although longer courses may be necessary. Dose and duration adjustments are necessary because of its renal excretion. The addition of hyperimmune globulin may be beneficial for patients with organ involvement. Foscarnet and cidofovir may also be used. DNA PCR can be used to evaluate response to treatment [78]. Inadequate response could indicate ganciclovir resistance necessitating further evaluation and foscarnet therapy. In addition, co-infections with CMV are not uncommon and should be considered.

Preemptive therapy of CMV infection has been advocated for solid organ transplant recipients. With this strategy, patients are monitored frequently and treated for CMV infection prior to development of symptoms. This method avoids complications and cost of drug therapy in low-risk patients and initiates treatment early to lessen symptomatic disease in high-risk patients. Preemptive strategy has been reported alone, compared to deferred treatment, and compared to prophylaxis [37, 79, 80]. CMV infections occurred more often in the preemptive group (75%) compared to the prophylaxis group (41%). No difference in symptomatic infections or mortality occurred in either of the pairings, although these were small studies. Deferred therapy was less expensive than preemptive therapy, and preemptive therapy was less expensive than prophylactic therapy. Guirado and colleagues [79] found that 2/3 of D+/R– patients developed antigenemia and all four of these patients progressed to serious disease that might have been prevented with prophylaxis of this high-risk group.

Prophylactic therapy with antiviral agents such as oral acyclovir, IV ganciclovir, IV immunoglobulin preparations such as hyperimmune CMV immunoglobulin (Cytogam) or standard pooled immunoglobulin have been used to control CMV infection, but are associated with variable efficacy and significant expense. High-dose oral acyclovir, 800 mg PO five times/day, was initially reported to prevent CMV disease in renal transplant patients [32]. However, we, as well as others, have shown that high-dose oral acyclovir does not prevent CMV disease in high-risk renal transplant recipients, and its use is associated with substantial cost and potential toxicity [34, 81]. Ganciclovir prophylaxis has been proven superior to acyclovir and less expensive than immunoglobulins [33, 82].

In a trial of 42 renal transplant recipients at risk for CMV infection, we showed that oral ganciclovir was highly effective for the prevention of CMV infection and disease [37]. In that study we compared ganciclovir 1,000 mg PO three times daily (n = 19) to our deferred therapy in which recipients received acyclovir 200 mg PO twice daily (n = 23) for 12 weeks for herpes simplex prophylaxis. The time to development of CMV disease was delayed by prophylactic oral ganciclovir (133 17 days versus 51 7 days; $p < 0.0001$). In the ganciclovir and deferred groups, respectively, 2/19 (11%) versus 23/23 (100%) developed CMV viremia by PCR during the period of prophylaxis ($p < 0.0001$). After discontinuing oral ganciclovir, 11/19 (58%) additional patients in the ganciclovir group subsequently developed PCR evidence for CMV viremia. Thus, 13/19 (68%) in the ganciclovir group versus 23/23 (100%) in the deferred group had evidence for CMV viremia by PCR at any time during the study ($p = 0.005$). This study in combination with others has shown that prophylactic treatment of CMV with ganciclovir delays the onset of CMV infections, reduces CMV infections, reduces severity of CMV disease, decreases acute rejection episodes, improves graft survival, and reduces steroid resistant rejection [36, 82, 83, 84]. It further suggests that prolonged pro-

phylaxis for six months to one year may be necessary when the donor is seropositive.

A recent large randomized study comparing prophylactic valacyclovir (8 g/d) to placebo for 90 days in 208 D+/R– patients and 408 R+ patients produced findings comparable to ganciclovir [65]. The finding included a delayed onset of CMV disease, a reduction in CMV infection and disease, and a decrease in biopsy confirmed acute graft rejection. Valacyclovir (3 g/d) has also been evaluated in a non-randomized uncontrolled study with similar findings but without the neurological side effects [85]. These preliminary data appear promising although further studies are needed to determine the role of valacyclovir in the prophylaxis and treatment of CMV. Finally, valganciclovir currently is being evaluated for prophylaxis and treatment of CMV.

Valganciclovir is a valyl-ester prodrug of oral ganciclovir, which has recently received FDA approval for the treatment of CMV retinitis in patients with AIDS. Valganciclovir has a bioavailability of nearly 70% (compared to 7% for oral ganciclovir) and at doses of 450 – 900 mg produces ganciclovir levels that are similar to intravenous administration of ganciclovir at 2.5 – 5 mg/kg [86]. The 6-month results of the Phase III PV16000 international, double-dummy, double-blinded trial of oral valganciclovir versus oral ganciclovir for the prevention of CMV in solid organ transplant recipients have recently been reported by Paya, CV, for the PV16000 Study Group, at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 27 – 30, 2002, San Diego, California. In this study 372 CMV D+/R– solid organ transplant recipients were randomized 2 : 1 to receive oral valganciclovir 900 mg per day or oral ganciclovir 1,000 mg 3 times per day with dose adjustments for renal insufficiency for 100 days as prophylaxis for CMV. Study medication had to be initiated within 10 days of transplant. There were 185 liver, 120 kidney, 56 heart, and 11 kidney-pancreas transplant recipients. All patients with CMV disease had a positive determination of CMV in blood or tissue. During prophylaxis only 0.8% and 1.6% of the patients developed CMV disease. Thus, this study did not show a significant difference between valganciclovir compared oral ganciclovir and reaffirmed that a period of intravenous ganciclovir is not necessary for adequate prophylaxis for CMV when an appropriate oral agent such as valganciclovir or ganciclovir is used. However, CMV disease occurred quite commonly after prophylaxis as we, and others, have reported. At 6 months, overall, in the valganciclovir and oral ganciclovir groups, respectively, CMV disease occurred in 12% vs 15% according to an FDA-adjudicated determination of CMV disease and 23% vs 22% according to the investigator-treated determination. In kidney transplant recipients, the intention-to-treat incidence of disease was 6% vs 23% and in the investigator-treated determination 20% vs 21% in the valganciclovir and oral ganciclovir arms, respectively. The greater incidences reported in the investigator-treated determination are much more consistent with historical reports and clinical experience.

During the PV16000 study, plasma was obtained at routine intervals and retrospectively analyzed for CMV by PCR. During prophylaxis 2.9% of those randomized to valganciclovir were viremic and 10.4% of those randomized to oral ganciclovir were viremic. These results suggest that valganciclovir prophylaxis may be less likely to induce ganciclovir resistance. By six months approximately 55% had become viremic in plasma. The incidence of viremia may have been greater if buffy coats rather than plasma were analyzed as leukocytes are a reservoir for

CMV. These results also suggest that 100 days of CMV prophylaxis may be insufficient for CMV D+R– transplant recipients.

Human Herpesvirus 6

HHV-6 is a -herpesvirus like CMV with two major subtypes, variant A and B. HHV-6B causes roseola infantum, or exanthema subitum in children. Infections from HHV-6A require further evaluation. Nevertheless, most HHV-6 infections are minor, self-limited, febrile illnesses, often followed by a rash. By two years of age, 90% of children are infected. In an immunocompetent host, the virus may be secreted in saliva, which is the likely mode of transmission. However, it remains latent in lymphocytes and is usually benign. In renal transplant recipients, reactivation of HHV-6 is frequent and ranges from 4 – 66%, but this variability is confounded by different diagnostic techniques and population seroprevalence [87, 88]. HHV-6 reactivation is associated with primary and reactivated CMV infections and symptomatic CMV infections [88, 89]. Unfortunately, these studies did not control for HHV-7. Also, HHV-6 infection can present as a CMV-like illness without CMV reactivation. It has been reported to cause hepatitis, encephalitis, and a hemophagocytic syndrome in a renal transplant recipient [90]. Reports of therapy against HHV-6 are limited, but ganciclovir, foscarnet, and cidofovir are potentially effective. Ganciclovir has been used for treatment and prophylaxis in non-renal transplant patients [39].

Human Herpesvirus 7

HHV-7 is also a -herpesvirus like CMV and HHV-6. It is ubiquitous and seroprevalence ranges from 60% to over 90%. HHV-7 has been associated with roseola and pityriasis rosea in children. Although often clinically similar, HHV-7 infections tend to occur after HHV-6 [91]. Reactivation in renal transplant patients is common and has been associated with progression to CMV disease and rejection [87, 92, 93]. Co-infection of HHV-7 and CMV has been treated with ganciclovir with resolution of HHV-7 viremia [93], but in general ganciclovir has minimal in vitro activity against HHV-7 [94] and is ineffective as prophylaxis [38]. Of the available agents, cidofovir is the most likely to be effective [94].

Human Herpesvirus 8

HHV-8, a recently discovered herpesvirus, is the cause of Kaposi's sarcoma (KS), multifocal Castleman's disease, and primary effusion lymphoma. Unlike HHV-6 and HHV-7, the seroprevalence in the US is < 3% and shows marked geographic variation with seroprevalence > 25% in Italy and regions of Africa [95]. Seroconversion of HHV-8-negative patients post-transplantation likewise is variable with rates as high as 12% [96]. HHV-8 is primary transmitted via sexual contact but also can be acquired from the donated kidney [97, 98]. The development of transplant-associated KS occurs both in patients seropositive prior to transplantation and in patients who seroconverted [96, 99]. It has been suggested that KS develops as a result of reactivation in endemic regions and from donor transmission otherwise [96]. The incidence of KS in transplant recipients is 0.1 – 5% and varies by regional prevalence [100]. The disease tends to occur within the first three years after transplantation and often is aggressive. Reduction in immunosuppression may lead to regression of the tumor but predisposes to rejection and

loss of the graft. Traditional therapies include radiation and cytotoxic regimens. In HIV-infected patients, foscarnet has been shown to slow progression of KS lesions [101] and ganciclovir reduced the incidence of KS [102]. Prophylaxis of CMV with ganciclovir may reduce the incidence of KS in renal transplant patients as well.

Hepatitis Viruses

Hepatitis A virus is a fecal-oral transmitted virus that rarely causes fulminant hepatitis. The hepatitis A vaccine has been evaluated in renal transplant patients. 24% of renal transplant patients seroconverted after the first dose and 72% after the second dose compared to 90% and 100% of controls, respectively [16]. When re-evaluated after two years, only 26% maintained protective antibody levels [103]. These results emphasize the need for pre-transplant immunizations and re-evaluation for at-risk patients despite prior vaccination.

Hepatitis B virus is a DNA virus commonly seen in dialysis and transplant patients that may remain latent, progress to cirrhosis, or cause fulminant hepatitis. It can occur in transplant patients as a result of primary infection, reactivation, or donor transmission. Controversy exists regarding the impact of HBV serostatus of the donor and recipient on transplantation as well as patient and graft survival. The role of HBV in renal transplantation was reviewed recently [104, 105]. Concern for reactivation of HBV during immunosuppression exists as HBsAg– but HBsAb+ and HBcAb+ patients have developed reactivation and hepatitis. Likewise, recipients from HBsAg– but HBcAb+ donors have seroconverted but without evidence of active infection. The risk of progression to active infection is higher if HBsAg+ is noted in the donor or recipient prior to transplantation. The effect of HBsAg+ status on mortality in transplant patients is controversial, but HBsAg– serostatus likely imparts a long-term survival advantage [106]. This difference may be secondary to pre-existing liver disease prior to transplantation, emphasizing the need for pre-transplant liver biopsy. The use of lamivudine as preemptive, prophylactic, and salvage treatment improves survival but long-term studies are needed [107, 108, 109]. The use of HBcAb+ donor kidneys has been evaluated and is considered safe in vaccinated patients and those with evidence of prior HVB infection [20, 21]. Interestingly, ganciclovir [110] and famciclovir have been used for treatment of HBV, but their prophylactic benefit is unclear.

Hepatitis C virus is a single-stranded RNA virus and the major cause of liver disease after renal transplant. The prevalence of HCV varies by geographic region and center from 10 – 41%, which is about 10 times that of the general population [111]. The majority of anti-HCV antibody-positive patients are also HCV RNA-positive, and patients may be HCV RNA-positive but lack an antibody response because of the humoral immunosuppression. The virus is transmitted parenterally and in most cases acquired from hemodialysis. Seroconversion after transplantation of a HCV RNA-positive donor kidney is nearly universal. Whereas anti-HCV antibody-positive but HCV RNA-negative kidneys rarely cause infection. Because of the shortage of donor organs, these anti-HCV antibody-positive kidneys are considered for HCV RNA-positive recipients [22]. Over 60% of HCV-infected renal transplant patients will develop chronic hepatitis [112]. The presentation may be subtle with normal liver function test and evidence of inflammation is found only on biopsy. This benign presentation requires

long-term follow-up to demonstrate an increased mortality. Mathurin and colleagues [106] showed after 10 years patient and graft survival of 65% and 49%, respectively, for HCV-positive recipients compared to 80% and 63% HCV-negative recipients. Besides progression to liver cirrhosis, other potential complications of HCV include fibrosing cholestatic hepatitis, hepatocellular carcinoma, cryoglobulinemia, membranoproliferative glomerulonephritis, membranous glomerulonephritis, and thrombotic microangiopathy. Treatments for HCV include interferon- , ribavirin, and amantidine. However, none of these treatments is both safe and effective after transplantation. Therefore, in renal transplant candidates, pre-transplant evaluation for HCV, liver biopsy, and treatment are critical.

Hepatitis G virus (HGV) is a recently discovered RNA virus of the Flaviviridae family. It is common in renal transplant patients with prevalence as high as 40 – 50% [113, 114]. It appears to have a low risk of chronic liver disease. De Filippi and colleagues [115] found that 14% of HGV carriers had persistently elevated alanine aminotransferase compared to 60% of HCV carriers. An association with HCV has been suggested but further studies are required.

Other Viruses

Adenovirus

Adenovirus is a common cause of pharyngitis, conjunctivitis, and respiratory infection. It occurs throughout the year with periodic outbreaks. It has been associated with hemorrhagic cystitis, hemorrhagic pyelonephritis, allograft dysfunction, liver necrosis, and fatal dissemination in kidney transplant recipients [116, 117, 118 119, 120]. In general the infection is self-limited but when necessary, reduction in immunosuppression may lead to resolution [117].

Respiratory Syncytial Virus

Respiratory syncitial virus (RSV) commonly occurs in children but is seen in adult renal transplant recipients as well. Infections typically occur between November and April and present initially as upper respiratory tract infections. However, the infection can progress to a lower respiratory tract infection with bilateral pulmonary infiltrates. It is usually diagnosed by nasopharyngeal swab. The treatment of RSV is supportive. However, inhaled ribavirin has been successful for severe pneumonitis in renal transplant patients [121]. The combination of RSV immunoglobulin and ribavirin appears effective in bone marrow transplant patients when began early [122, 123]. Palivizumab, a humanized monoclonal antibody against RSV, is only approved for children but it appears safe and well-tolerated in stem cell transplant patients [124].

Influenza

Influenza is a major cause of acute respiratory illness and affects immunocompromised individuals more severely than immunocompetent individuals. In addition to the typical viral prodrome of fever, headache, myalgias, and dry cough, influenza has been associated with viral pneumonia, secondary bacterial pneumonia, rhabdomyolysis, and multiple neurological complications including encephalitis and hemolytic uremic syn-

drome [125, 126]. It is recommended that transplant patients, their family, and transplant personnel receive yearly vaccinations for influenza. However, for non-vaccinated patients, those with egg allergies and vaccine failures, two classes of drugs are available for prophylaxis and treatment: M2 blockers including amantadine and rimantadine and viral neuraminidase inhibitors including zanamivir (Relenza) and oseltamivir (Tamiflu). Care should be taken in patients with decreased renal function since all four drugs are cleared through the kidneys.

Human Immunodeficiency Virus

Infection with the human immunodeficiency virus (HIV) has been considered a contraindication to renal transplantation until recently. Prior to the use of highly active anti-retroviral therapy (HAART), the concern of unchecked viral replication from immunosuppressive regimens and accelerated progression of a fatal disease led to a general consensus to reserve a limited supply of donor kidneys to those most like to benefit, non-HIV-infected patients. Almost 90% of transplant centers surveyed would not transplant a patient with HIV [127]. This strategy was based on studies that showed HIV-positive renal transplant patients rapidly progressed to the acquired immunodeficiency syndrome (AIDS) and had a higher mortality compared to HIV-negative renal transplant patients and HIV-positive hemodialysis patients [128, 129]. However, other studies did not confirm these findings [130, 131]. Since the use of HAART, HIV patients survive longer and suffer less opportunistic complications. Now they face other challenges including ESRD from HIV-associated nephropathy. The number of HIV patients on hemodialysis for ESRD is increasing and hemodialysis increases mortality in HIV patients [132, 133]. With a wider array of immunosuppressive medications, antibiotics, infectious disease detection methods, and prophylactic strategies, HIV patients will like see a mortality and morbidity benefit from kidney transplantation compared to hemodialysis. Preliminary data from a study by Roland and Stock [134] demonstrated a 91% and 71% one-year patient and graft survival, respectively, in patients with well-controlled HIV. Although below the survival for non-HIV-infected patients, this preliminary data are very encouraging and represent an advance in this emerging aspect of transplant nephrology. Many complexities will arise as transplantation into HIV-positive recipients becomes more common including pre-transplant screening for appropriate level of viral suppression and estimating risk of progression to AIDS, polypharmacy with medication interactions, possible recurrence of HIV-associated nephropathy, and infection surveillance and management with a doubly compromised immune system.

Polyomaviruses

The polyomaviruses (simian virus 40, JC, BK) are double-stranded non-enveloped DNA viruses that can lead to nephropathy (PVN) and graft failure. Exposure to simian virus 40 (SV40) likely occurred from contaminated poliovirus vaccines, whereas BK and JC are ubiquitous human viruses. Originally, BK was found to cause ureteral strictures in renal transplant patients and hemorrhagic cystitis in bone marrow transplant patients. JC is the agent responsible for progressive multifocal leukoencephalopathy (PML). Since 1995, BK has been implicated as the cause of renal

dysfunction with the histological presentation of interstitial nephritis often mimicking acute rejection [135]. BK nephropathy occurs in up to 7% of transplant recipients [136] and can cause graft loss in up to 45% [137].

Co-infection with SV40 and BK [136] and JC and BK [138] in PVN occur, although their contribution to PVN is likely minimal. PVN is diagnosed by detection of BK on biopsy, although BK viral load in plasma may act as a surrogate [139]. Once PVN is detected, the management is reduction of immunosuppression. Cidofovir has been used with variable success [140, 141]. Screening methods to detect the reactivation of BK prior to overt nephropathy include detection of decoy cells in the urine, viruria, and viremia. The role of screening and preemptive reduction in immunosuppression to prevent progression to PVN remains to be resolved.

West Nile Virus

The West Nile virus (WNV) is a single-stranded RNA virus within the genus Flavivirus. It is transmitted from mosquito to bird and back to mosquito. Humans and horses likely are dead end hosts [142]. Other modes of transmission have included infected blood products, organ donation, and lab-acquired. Once infected, the incubation period is up to 2 weeks and most infections remain asymptomatic. The clinical presentation may include a transient flu-like illness in about 20% with less than 1% progressing to encephalitis. Diagnosis is made by detection of WNV IgM antibodies in serum or CSF [143]. Therapy currently remains supportive. Possible drug therapies include ribavirin, interferon- , and IVIG.

West Nile virus infections in the transplant population are rare. Hardinger and colleagues [144] recently reported two cases of established renal transplant recipients who developed community-acquired WNV. The patients presented with the typical symptoms of fever and mental status changes despite immunosuppression. With supportive care both patients returned to baseline function within one month. In another report [145], four patients who had received organs from a single donor previously transfused with an infected blood product became symptomatic between 7 and 17 weeks after transplantation. Three progressed to encephalitis and one died. Although not an established risk factor, the degree of immunosuppression likely contributes to the severity of WNV infection.

Human Papillomavirus

Human papillomavirus (HPV) causes a variety of cutaneous and mucosal lesions. HPV has been associated with cutaneous warts, actinic keratosis, non-melanoma skin cancers, condyloma acuminatum, verrucous carcinoma, bowenoid papulosis, intraepithelial anogenital neoplasia, and laryngeal and urethral papillomatosis. In renal transplant recipients, cutaneous warts are often multiple, located on the hands and arms, and increase in frequency over time (15% at 1 year and 85% at 5 years) [146]. The role of HPV, if any, in carcinomas of the skin is unclear. In one study [147], renal transplant recipients were divided into high, intermediate, and low susceptibility groups based on the number and type of skin lesions. Those with high susceptibility had an increased prevalence of HPV DNA in skin lesions and a higher risk for anogenital malignancies. This data emphasizes the need for cancer screening, especially in the highly susceptible patients, since renal transplant recipients are known to have a

higher incidence of intraepithelial and invasive neoplasia of the anogenital tract [148, 149]. Treatment is primary ablative but local antiviral and immunomodulatory agents have been effective [150]. Prevention involves use of barriers to prevent transmission and avoidance of high-risk sexual practices. Vaccines are under investigation for prevention of HPV infection and appear promising [151, 152].

Fungal Infections

Systemic fungal infections occur in 2% to 14% of renal transplant recipients [153, 154, 155, 156]. Although systemic mycoses encompass a broad range of diseases, about 2/3 of patients die from the infection [153, 154, 156, 157]. The increased rate of infections may be due to environmental factors such as poor sanitation and greater endemic burden, a compromised immune system with impaired phagocytosis and cellular immunity, and alterations of the endogenous bacterial flora. Risk factors for development of systemic fungal infections include age, prolonged hospitalization, medications like broad-spectrum antibiotic and corticosteroids, comorbid conditions such as diabetes mellitus, liver disease, and CMV disease, and breaches in the innate defenses such as indwelling catheters, disruption of intestinal mucosa, and tissue ischemia [153, 156, 158, 159]. The clinical manifestations of these infections are often non-specific. Therefore, a high index of suspicion and an aggressive approach to diagnosis are important. Therapy includes specific antifungal agents and risk factor reduction, such as removing IV catheters and decreasing immunosuppression.

Candidiasis

Candidiasis is the most common fungal infection affecting renal transplant patients. *Candida albicans* is the usual causative pathogen. Other reported species include *C. tropicalis, C. krusei,* and *C. glabrata*. Candidal infections are generally manifest as mucocutaneous overgrowth including thrush, intertrigo, onychomycosis, esophagitis, or vaginitis. Invasive candidiasis usually occurs when the mucocutaneous barrier is breached for example, bladder and IV catheters or surgical trauma. This may present as catheter-related sepsis. The risk of hematogenous dissemination is 10-fold higher in immunosuppressed patients compared to normal hosts. Manifestations of disseminated (often metastatic) candidal infections are diverse, and include skin lesions, intra-abdominal abscesses, meningitis, brain abscess, endophthalmitis, endocarditis, aortitis, arthritis, osteomyelitis, pneumonitis, pyelonephritis, and urinary tract obstruction (fungus balls). Diagnosis of candidal infections in renal transplant recipients is made by performing fungal stains and cultures of appropriate specimens, usually tissue biopsies.

Treatment of candidal infections depends on the location, *Candida* species, and prior treatment therapies. In general, oral, vaginal, and cutaneous candidiasis can be treated by topical therapy with either nystatin or clotrimazole. Oral fluconazole is generally effective for esophagitis, UTI, or topical therapy failure. Asymptomatic candiduria should be treated in post-transplant patients after removal of the bladder catheter because of the use of high-dose immunosuppressives, bladder dysfunction, and frequent underlying diabetes [160]. In addition, this finding may be the only evidence of disseminated disease. Invasive candidal infections require removal of foreign devices and prolonged IV antibiotic

therapy. Recommended therapy includes either IV fluconazole or amphotericin B until organ involvement resolves [161]. *Candida albicans, C. tropicalis,* and *C. parapsilosis* are typically susceptible to fluconazole, while *C. glabrata* and *C. krusei* often are resistant. Two new agents, voriconazole, an azole, and caspofungin, an echinocandin, are available and have been used to treat fluconazole-resistant *Candida* species.

The use of antifungal agents in renal transplant patients requires frequent monitoring. The azole antifungals inhibit the cytochrome P450 system and increase levels of cyclosporine, tacrolimus, and sirolimus. Caspofungin was associated with elevated liver transaminases when used in combination with cyclosporine. Finally, amphotericin B is the drug of choice for critically ill patients even though it is well-known to be nephrotoxic. The liposomal formulations of amphotericin B appear to have less and delayed nephrotoxicity and may be preferred for patients with renal insufficiency or being treated with nephrotoxic medications such as cyclosporine.

Cryptococcosis

Cryptococcus neoformans is the most common cause of CNS fungal infection in kidney transplant patients. *C. neoformans* is present in soil contaminated with bird excreta. Infections are acquired by inhalation and occur in 0.3 – 4% of renal transplant recipients [154, 162, 163, 164, 165]. In the immunocompromised host, the fungus quickly can disseminate from the lungs. The most common sites of isolated infection are the CNS (55%), skin (13%), and lungs (6%) [164]. The majority of cases of cryptococcal meningitis occur after six months following transplantation. The presentation is generally subacute or chronic, and symptoms include fever, headache, mental status changes, and focal neurologic deficits. Cutaneous involvement may be manifested as a cellulitis, nodular skin lesion, and an acneiform eruption. Cryptococcal pneumonia may be indistinguishable from other community-acquired pneumonia.

Diagnosis is made by performing an India ink stain and culture of tissue aspirates. Detection of cryptococcal polysaccharide antigen in the serum likely indicates invasive fungal infection. The finding of an elevated opening CSF pressure during lumbar puncture is suggestive of cryptococcal meningitis and can be confirmed with a positive cryptococcal antigen test.

Treatment with amphotericin B and 5-flucytosine is most effective for acutely ill patients. Less severe infections have been successfully managed with fluconazole. Tacrolimus has anti-cryptococcal activity and is associated with more skin infections and less CNS infections compared to non-tacrolimus based regimens. One possible explanation is that tacrolimus has better CNS penetration compared to cyclosporine and its antifungal activity decreases with decreasing temperature [164].

Aspergillosis

The most common cause of aspergillosis is *Aspergillus fumigatus*. However, other species, including *A. flavus* and *A. niger*, can cause disease. The fungus is ubiquitous in the environment and is readily aerosolized. Inhalation of spores results in infections of the respiratory tract and a means of dissemination. Infection is rare except in immunocompromised patients but occurs in up to 3% of renal transplant recipients [153, 155, 156, 157,

166]. Infections usually occur during the first 3 months following transplantation but nosocomial outbreaks have been associated with hospital construction and renovation. Characteristic presenting symptoms include fever, cough, hemoptysis, and pleuritic chest pain. The pathology consists of a necrotizing bronchopneumonia with small vessel invasion and hemorrhage. Disseminated aspergillosis most often involves the CNS and is manifest as meningitis, encephalitis, brain abscesses, or granulomas. Symptoms are non-specific and include headache, altered mental status, seizures, and evolving stroke. Other organs that may be affected include the gastrointestinal tract (GI), kidneys, liver, thyroid, heart, pericardium, spleen, bones, and joints. Risk factors for invasive aspergillosis include renal failure, immunosuppression (high-dose corticosteroids and antilymphocyte antibody), neutropenia, and CMV infection [167, 168].

The key to diagnosis is clinical suspicion and demonstration of *Aspergillus* in tissue biopsy or aspirate and growth in culture. Detection of *Aspergillus* in the respiratory tract (sputum, nasal swab, and bronchoalveolar lavage) is very suggestive of disease in immunocompromised patients. Also, the characteristic radiographic findings of wedge-shaped pleural-based densities or cavities on CXR and the "halo sign" on CT may aid in early invasive diagnosis and treatment.

Disseminated aspergillosis has a poor prognosis and a mortality approaching 100%. Amphotericin B has been the standard therapy, often requiring high dosing regimens for long periods. However, lipid soluble formulations of amphotericin B have comparable efficacy but reduced renal side effects [169, 170]. Voriconazole was shown to improve survival (70.8% vs 57.9%) at 12 weeks with fewer severe side effects compared to amphotericin B [169, 170, 171]. Itraconazole is also approved for amphotericin B refractory or intolerant patients. Caspofungin has been approved as salvage therapy for invasive aspergillosis [172]. In addition to medical therapy, surgery may be required to remove necrotic tissue and localized infections.

Mucormycosis

Infections with fungi of the class *Zygomycetes* cause mucormycosis. This class includes *Rhizopus* species, *Mucor* species, *Absidia* species, *Rhizomucor* species and *Cunninghamella* species. These fungi are ubiquitous found in food, air, and soil. Infection is uncommon although occurs with a prevalence of 0 – 1.2% [157] in renal transplant recipients. Risk factors include diabetic mellitus, chelation therapy with deferoxamine, corticosteroids, and hematologic malignancies. Similar to *Aspergillus*, fungal spores are inhaled into the respiratory tract, hyphae invade the small vessels causing hemorrhage and infarction, and then the fungus can disseminate. Clinical manifestations include rhinocerebral, pulmonary, cutaneous, CNS, and GI involvement. Signs and symptoms of infections are non-specific and can present as fever, orbital cellulitis, ophthalmoplegia, hemoptysis, cough, chest pain, headache, mental status changes, and GI bleeding [173]. Diagnosis is made by tissue biopsy and histologic examination. Treatment consists of aggressive surgical debridement of necrotic tissue, minimizing risk factors, and antifungal therapy with amphotericin B. Rapid diagnosis and treatment of patients at risk are critical because of the high morbidity and mortality (80%) [174] associated with mucormycosis.

Endemic Mycoses

These infections can occur at any time following transplantation. Histoplasmosis and coccidioidomycosis are more common in transplant patients and are caused by *Histoplasma capsulatum* and *Coccidioides immitis*, respectively. The clinical presentation of these mycoses is varied and dissemination is common.

Histoplasmosis

Histoplasmosis is endemic in the central United States and is acquired by inhalation. Infection with *H. capsulatum* occurs in 0.4 – 2.1% of renal transplant recipients [175, 176]. Most cases represent primary exogenous infection. Histoplasmosis can be transmitted from the organ donor, and reactivation of latent foci can occur. Thus, the presence of clinical disease should be evaluated in potential transplant recipients who are seropositive for *H. capsulatum*, and post-transplant prophylaxis with itraconazole should be considered.

Histoplasmosis is disseminated in 60 – 90% of patients and the symptoms and signs are non-specific. These include fever, night sweats, fatigue, weight loss, and cough. The CXR may be normal in as many as 50% of cases, or show diffuse or miliary infiltrates, hilar adenopathy, or pleural effusions. Other manifestations include diverse cutaneous lesions, hepatosplenomegaly, CNS disease, adrenal and musculoskeletal lesions.

A high index of suspicion and a thorough travel history are important in making the diagnosis. Bone marrow cultures are positive in > 90% of cases but may take as long as 2 – 6 weeks. Therefore, methenamine-silver staining of blood, bone marrow or other affected tissues often yields a more rapid diagnosis. Other useful diagnostic techniques include serologic testing and antigen detection in blood, urine, or other body fluids. Treatment with amphotericin B is very effective. An alternative agent is itraconazole for patients who cannot tolerate amphotericin B or only have mild disease. Antigen levels can be followed to monitor response to therapy and predict relapse. Consideration should be given to chronic suppressive therapy.

Coccidioidomycosis

Coccidioidomycosis is endemic in the southwestern United States, northern Mexico, and regions of Latin America. Patients who have lived in or traveled to these areas are at increased risk of infection with *C. immitis*. The majority of cases can be attributed to reactivation of old foci of infection, and occur within the first year post-transplant. However, coccidioidomycosis can result from a primary infection and may occur at any time in an immunosuppressed host [177].

Transplant recipients infected with *C. immitis* usually develop progressive disseminated disease associated with a high mortality. Risk factors for dissemination include male sex and blood group B [178]. Presenting complaints include fever and cough and chest X-ray findings are diverse, including hilar adenopathy, infiltrates (nodular, alveolar, lobar), miliary, and, rarely, cavitary disease. Other sites of involvement include the skin, joints, central nervous system, liver, and kidney.

Diagnosis of coccidioidomycosis is made by histologic examination of biopsy tissue, culture of blood, bone marrow or other body fluids, or serology. Coccidioidin skin testing is usually negative. Treatment is with

fluconazole or amphotericin B for severe disseminated disease. This should be followed by long-term suppressive therapy with fluconazole or itraconazole.

Pneumocystosis

Pneumocystis carinii is an extracellular organism resembling both fungi and a protozoan parasites. Approximately 10% of kidney transplant recipients not receiving prophylactic therapy develop *Pneumocystis carinii* pneumonia (PCP), usually in the first six months after transplantation. In non-immunocompromised hosts, *P. carinii* has low virulence. This is enhanced by pharmacologic immunosuppression and coexistent infection with certain viruses, such as HIV and CMV [179, 180].

The clinical presentation of PCP is subacute with symptoms of fever, non-productive cough and dyspnea, interstitial infiltrates on chest X-ray, and hypoxemia out of proportion to either physical or radiographic findings. The diagnosis is made by identifying the *P. carinii* in induced sputum (30 – 55% yield), bronchoalveolar lavage fluid (> 50% yield), or, rarely, a lung biopsy specimen (> 90% yield). A variety of techniques can be used to detect the organism, immunofluorescent monoclonal antibody (IF) against surface epitopes of *P. carinii* or toluidine blue O staining typically is used for bronchoalveolar lavage fluid. Giemsa, Gomori methenamine silver, Wright's, toluidine blue O, periodic acid-Schiff and Papanicolaou stains can be used for tissue. PCR assays for PCP are the most sensitive and may be useful for suspected cases of PCP with negative IF [181, 182].

The drug of choice for initial treatment of PCP is TMP-SMX (15 mg/kg/day TMP/75 mg/kg/day SMX) for two weeks. For patients who have failed or are intolerant of TMP-SMX, second-line therapy is with IV pentamidine (4 mg/kg/day). Alternative agents include trimetrexate plus folinic acid, trimethoprim plus dapsone, atovaquone, or primaquine plus clindamycin. Frequent adverse effects of pentamidine include renal dysfunction, hypotension, hypoglycemia, blood dyscrasias, and gastrointestinal disturbances [183]. Concurrent bacterial or CMV infection should be treated as well. Prophylactic therapy with low-dose TMP-SMX (1 double-strength tablet daily) is very effective at preventing *P. carinii* infection in immunosuppressed patients, and treatment should be continued for at least 6 – 12 months post-transplant [184, 185]. If discontinued, prophylaxis should be resumed in the setting of increased immunosuppression. Alternative preventative strategies include aerosolized pentamidine (300 mg monthly) or oral dapsone (50 – 100 mg daily).

Mycobacterial Infections

Mycobacterium Tuberculosis

Approximately 1 – 15% of renal transplant recipients develop active *M. tuberculosis* infection (TB) and prevalence varies by geography and endemicity [186, 187, 188, 189, 190, 191]. The lowest incidence is in North America and the highest in India. The majority of TB occurs within the first year post-transplant, although it can occur at any time following transplantation [192, 193]. Immunosuppressed patients are at increased risk for both primary infection and reactivation. Transmission of *M. tuberculosis* from the renal allograft has been reported. TB can effect almost any organ system, but it most

commonly presents either as pulmonary disease or as disseminated disease. The GI tract is the most common extrapulmonary site. Clinical manifestations include fever, weight loss, pulmonary disease with focal infiltrates (40%) or a miliary pattern (22%) on CXR [192], GI involvement most commonly in the ileocecal region, osteomyelitis, septic arthritis, cutaneous lesions, meningitis, nephropathy, and lymphadenitis. Risk factors for active tuberculosis include non-Caucasian race, aging, malnutrition, DM, CMV, renal failure, liver disease, co-existing infections, upper gastrointestinal surgery, a history of inadequately treated disease, and immunosuppressive therapy. Mortality in renal transplant patients is 30% overall and is greatest in disseminated TB.

Evaluation for *M. tuberculosis* infection in kidney transplant patients should begin pre-transplant. Risk factors should be queried including high-risk exposures, prior positive PPD, and prior treatment. A positive PPD in patients with chronic renal failure is > 10 mm. A PPD > 5 mm is considered positive with CXR evidence of prior TB infection or close contacts of TB cases. These patients require further evaluation for evidence of active disease. Patients with latent disease should undergo treatment prior to transplant to prevent reactivation and medication interactions. After transplantation, a positive PPD is > 5 mm [194]. Use of the QuantiFERON-TB test for diagnosis of latent or active TB is not recommended in the pre- or post-transplant setting [195]. Patients suspected of having active tuberculosis should be isolated to avoid transmission to other susceptible hosts. Three induced sputum specimens should be obtained in the early morning and sent for acid-fast stain and culture. Bronchoalveolar lavage fluid and post-bronchoscopy sputum samples can also be sent for acid-fast stain and culture. In the case of extrapulmonary disease, other body fluids (pleural, ascitic, cerebrospinal, synovial, urine, or other) should be concentrated prior to staining. Histopathologic examination of biopsy tissue (acid-fast bacilli and granulomata) may also be useful if disease is suspected and body fluid analysis is non-diagnostic. Rapid assay kits are also available and utilize nucleic acid amplification techniques to detect the organism.

Patients with latent TB require treatment with isoniazid (INH) for nine months. Alternative therapies including INH for six months, rifampin and pyrazinamide for two months, and rifampin for four months can be considered because of adverse effects, drug interactions, high cost, or poor compliance [194]. Because of the high prevalence of drug-resistant *M. tuberculosis*, active TB should be treated with directly observed therapy consisting of a 2-month initial phase of INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Alterations to this regimen are allowed if drug susceptibilities are known in advance and for certain underlying medical conditions. After two months, the regimen can be tailored based on the drug sensitivities and continued for 4 – 7 months [196]. Renal transplant recipients receiving treatment for active or latent TB should be followed closely and liver enzymes should be checked because of the high prevalence of liver disease and possible drug interactions. The adverse effects and toxicity of anti-tuberculous agents are well described. One effect, of particular importance to patients receiving immunosuppression, is that INH and rifampin induce hepatic cytochrome P450 enzymes and increase the metabolism of glucocorticoids, cyclosporine, tacrolimus, and sirolimus. This can lead to under-immunosuppression and rejection if blood levels of immunosuppressive drugs are not followed closely.

Atypical Mycobacteria

Non-tuberculous mycobacteria (NTB) are ubiquitous and can infect renal transplant patients, usually late in the post-transplant period. Major risk factors include glucocorticoid therapy and impaired cell-mediated immunity. Typically, these infections are chronic and involve the skin and musculoskeletal system. Occasionally, pulmonary or gastrointestinal involvement is seen. Dissemination of *M. kansasii* can occur but is rare. Cutaneous disease is often caused by mycobacterial species *M. marinum, M. haemophilum*, and *M. chelonae*, and is manifest as painful erythematous or violaceous subcutaneous nodules that may ulcerate or become superinfected.

The key to diagnosis is a high index of suspicion when patients fail to respond to appropriate antimicrobial therapy. In patients with pulmonary findings, at least three sputum or bronchial washings should be sent for acid-fast staining and culture. Lesions should be aspirated or biopsied and tissue sent for histopathology, acid-fast staining and culture. DNA probes and high-pressure liquid chromatography are available for rapid species identification. Treatment for slow growing NTB is tailored to the species and location but typically include a combination of azithromycin or clarithromycin, rifampin or rifabutin, and ethambutol. Rapidly growing NTB is resistant to typical anti-tuberculous therapy but are susceptible to many traditional antibiotics [197]. Surgical resection and debridement often are necessary for extrapulmonary disease and poor response to medical therapy. The prognosis for non-disseminated atypical mycobacterial infections is generally favorable.

Conclusion

Approximately 2/3 of renal transplant recipients will experience an infectious related complication in the first year after transplantation. This reflects the overall, or net state, of immunosuppression associated with end-stage renal disease (ESRD) and transplantation as well as donor and environmental exposures. Renal transplant candidates often are immunosuppressed prior to transplantation from age, nutrition, comorbid conditions, and medications. After transplantation, immunosuppressive medications are used to maintain the donor kidney but further hinder the immune response. This difficult balance favors the reactivation and progression of infections. These infections may come from the donor kidney, transfused blood products, the environment, or occult and latent infections within the recipient. The intensity of the immunosuppressive regimen predisposes recipients to specific infections. As the intensity of therapy declines over the first year, the frequency of infections with specific agents changes as well. Understanding the degree of immunosuppression and the time course of infections aids in the diagnosis of infections and the appropriate use of preemptive, prophylactic and treatment strategies.

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Non-infectious Post-transplant Complications

Simin Goral and J. Harold Helderman

Renal transplantation has become a routine means of managing the need for renal replacement. Graft and patient survival rates are superb, greater than those for comparable patients awaiting a transplant on dialysis [1]. Death with a working transplant rivals loss of the allograft to chronic rejection as a cause of graft loss. Indeed, at many centers this cause of graft loss outstrips rejection, acute or chronic. Interestingly, the major causes of morbidity and mortality after the first year are due to disorders unrelated directly to immunologic etiologies or disease related to immunosuppressive drugs such as infections and neoplasms. Recognition of these facts, startling to some, makes imperative the understanding of the pathogenesis and management of non-infectious complications after renal transplantation. This chapter deals with these complications including hypertension, cardiovascular disease, hyperlipidemia, metabolic bone disease, and malignancy.

Hypertension

Hypertension, a well-known significant risk factor for cardiovascular disease, commonly afflicts the renal transplant recipient even in the face of restoration of renal function and volume control. The etiology of post-transplant hypertension is multifactorial (Table 1). Systemic blood pressure in transplant recipients can be greatly affected by the immunosuppressive agents such as steroids, cyclosporine or tacrolimus. The renin-angiotensin axis may be associated with hypertension with the transplanted kidney and/or the native kidneys the source. Other factors such as expansion of extracellular volume, hypercalcemia, acute or chronic rejection, renal artery stenosis, and recurrent or de novo glomerulonephritis in the allograft all contribute to posttransplant hypertension.

Table 1. Causes of Hypertension after Renal Transplantation

Immunosuppressive therapy
Cyclosporine A
FK506
Steroids
Allograft dysfunction
Chronic rejection
Nephrotoxicity (CsA, FK506)
Recurrent glomerulonephritis
De novo glomerulonephritis
Renal artery stenosis
Excessive weight gain
Hypercalcemia

Impact of Immunosuppression on Hypertension

It has been demonstrated that immunosuppressive therapy is an important contributor to post-transplant hypertension. Although substantial throughout the history of renal transplantation, the prevalence of hypertension increased significantly after the introduction of cyclosporine to organ transplantation. Among transplant patients treated with steroids and azathioprine, 49 – 64% of them developed hypertension at 1 year after transplantation [2, 3]. In 212 cyclosporine-treated renal transplant recipients, the prevalence of hypertension was reported as 81.6% at 1 year and 81.2% at 5 years after transplantation. Four patients who were converted from cyclosporine to azathioprine-prednisone based regimens had a significant improvement in their blood pressure [5].

Mechanisms of Cyclosporine-induced Hypertension

The pathophysiology of cyclosporine-induced hypertension is still unclear. Possible mechanisms are summarized in Table 2. Acute intravenous (IV) cyclosporine has been shown to be a potent stimulator of the renin-angiotensin system in animal models [6, 7]. On the other hand, examination of the renin-angiotensin axis in man after chronic oral use of cyclosporine finds most often suppressed renin levels as a function of urinary sodium excretion [8]. This paradoxical effect on renin elaboration suggests that renin-angiotensin is unlikely to contribute to the etiology of long-standing, fixed hypertension in the cyclosporine-treated renal transplant recipient. Cyclosporine directly increases renal vascular resistance, increases renal sodium retention and causes vasoconstriction of the afferent arteriole in both animals and humans. Endothelin, a potent vasoconstrictor, has been recently implicated in acute cyclosporine-induced vasoconstriction and hypertension. It has been shown that circulating levels of endothelin are elevated in animals as well as in humans treated with cyclosporine [9, 10]. In addition, there is evidence that chronic endothelin receptor blockade with bosentan, a nonpeptide endothelin receptor antagonist, lowers blood pressure in cyclosporine-treated hypertensive rats which supports the role of endothelin in early cyclosporine-induced hypertension [11]. In another study, striking preservation in glomerular filtration rate (GFR) and decreased vasoconstriction were present in animals treated with cyclosporine and an endothelin receptor antagonist, while there was no protection for structural damage [12]. These studies emphasized the importance of endothelin, a partial and early culprit in cyclosporine-induced vasoconstriction and thus hypertension. Whether anti-endothelin drugs that are currently being developed would be beneficial for patients who are on cyclosporine or not remains to be seen for the more chronic forms. Another mediator of vasoconstriction, thromboxane, has also been implicated in post-transplant cyclosporine-re-

Table 2. Possible Mechanisms of Cyclosporine-induced Hypertension

– Stimulation of renin-angiotensin system [6-8]
– Direct increase in renal vascular resistance [6–8]
– Increased renal sodium retention [18, 19]
– Volume expansion [18, 19]
– Vasoconstriction of the afferent arteriole [6–8]
– Increased levels of endothelin [9–12]
– Sympathetic nervous system activation [16]
– Reduction in nitric oxide [17]
– Increased intracellular calcium [20–22]
– Increased TGF-β in the graft [23, 24]

lated hypertension. Kawaguchi and colleagues reported an increase in urinary degradation products of thromboxane A_2, specifically thromboxane B_2 in cyclosporine-treated animals [13]. Unfortunately, therapy with inhibitors of thromboxanes in man has not been very successful [14, 15].

Another possible factor contributing to cyclosporine-induced post-transplant hypertension reflects enhanced response of the sympathetic nervous system to stimuli based on the observation of Scherrer et al. who demonstrated that cyclosporine treatment was accompanied by sustained sympathetic activation in heart transplant recipients [16]. This hypothesis would imply that vasoconstrictive sympathomimetic peptides are elaborated in excess in cyclosporine-treated patients increasing propensity for hypertension in response to a variety of stimuli.

Complicating an already complicated picture are the data implicating the nitric oxide (NO) system in the genesis of cyclosporine-induced hypertension. It has been proposed that cyclosporine-induced hypertension is partially related to impaired vasodilatation secondary to reduction in NO induced by cyclosporine. The inhibitors of NO, a physiological messenger molecule derived from the vascular endothelium and other cells of the cardiovascular system, may cause vasoconstriction and compromise blood flow distribution after ischemia [17].

In contrast to the paradoxical relationship of cyclosporine to mediators of hypertension as a function of acute or chronic observation, there is clear evidence for volume expansion in cyclosporine-treated recipients at all time points suggesting that sodium retention and volume are important contributors to clinically important hypertension. Transplant recipients treated with cyclosporine have enhanced proximal tubular sodium avidity and reabsorption causing an increase in intravascular volume, which turns out to be one of the major contributors to hypertension after transplantation [18, 19].

Increased intracellular calcium also plays an important role. In hypertensive humans and animals, intracellular calcium has been found to be elevated in several cell types, including platelets, red blood cells, and smooth muscle cells [20]. It has been shown that cyclosporine administration is associated with increased intracellular calcium in vascular smooth muscle cells increasing vasoconstriction [21, 22].

An interesting new finding is the correlation of human renal allograft interstitial fibrosis and chronic allograft nephropathy as well as post-transplant hypertension with intragraft expression of transforming growth factor-β_1 (TGF-β_1) [23]. As shown in Figure 1, increased TGF-β_1 production by ischemia, rejection and drugs (most commonly cyclosporine and steroids) stimulates endothelin-1 production contributing to post-transplant hypertension [24]. In summary, the pathogenesis of cyclosporine-induced hypertension after transplantation is multifactorial. Most of the time ≥ 2 factors are involved. There is strong evidence that vasoconstriction via endothelin, TGF-β_1, and increased intracellular calcium, renal sodium retention leading to increased intravascular volume, and increased sympathetic nerve activity seem to be the major contributors to cyclosporine-induced post-transplant hypertension.

Hypertension after transplantation has also been reported with the use of tacrolimus (FK506). In a recent multicenter study, the incidence of hypertension was similar in both cyclosporine-and FK506-treated patients (38.6% vs. 36.6%) [25]. FK506 has been shown to upregulate the endothelin receptor mRNA in blood vessels in rats suggesting a possible role for endothelin in the genesis of FK506-induced hypertension [26].

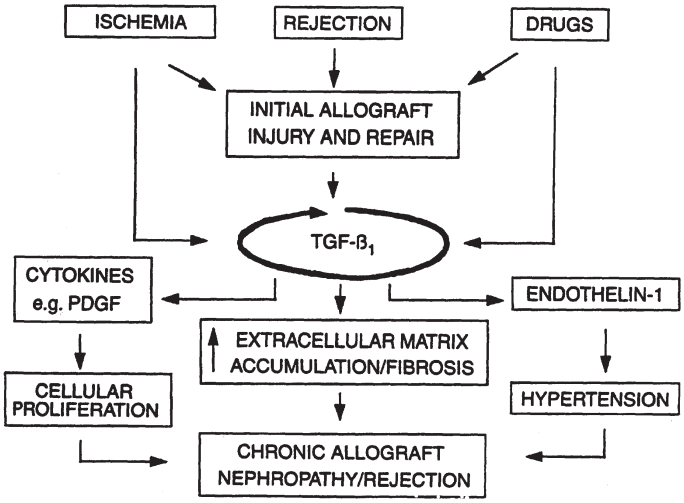

Figure 1. Schema for the pathogenesis of chronic allograft nephropathy and hypertension as constructed by Sharma et al.

Management of Post-transplant Hypertension

Although more basic research can help explicate the genesis of hypertension in the cyclosporine-treated transplant recipients, the 3 mechanisms for which unambiguous data exist, sodium retention, enhanced response to sympathomimetic stimuli, and increased intra-cellular calcium scientifically supports therapeutic modalities empirically observed to be most effective for blood pressure control. Calcium channel blockers have been shown to be most effective [27 – 29]. The selection of the class of the calcium-entry blocker depends on one's philosophic approach to the manipulation of the hepatic P450 microsomal system employed most frequently for metabolism of the parent cyclosporine molecule to inactive or less active end products. We at the Vanderbilt Transplant Center specifically choose the dihydropyridine class (e.g. nifedipine, nicardipine, amlodipine, isradipine, felodipine) since this class is least likely to occupy the P450 isoenzyme system important for cyclosporine degradation. Manipulation of dose to control blood pressure therefore should have less effect on cyclosporine blood levels. Others use the non-dihydropyridine class (e.g. verapamil, diltiazem) to reduce the cyclosporine dose needed to achieve immunosuppressive target blood levels while controlling blood pressure. If the latter choice is made, it is essential to monitor cyclosporine levels closely whenever the dose of the non-dihydropyridine class agents is altered, especially if the dose is reduced or the drug is completely stopped. Use of low-dose diuretics (choosing the one least likely to increase blood lipids) addresses the sodium retention which characterizes both cyclosporine and FK506. The third group of agents which can be added if needed for blood pressure control are those which blunt the impact of the sympathetic nervous system. Central-acting agents such as clonidine or alpha-receptor blockers are agents of choice, as they do not increase blood lipids. Lastly, a new consideration of the role of angiotensin-receptor blocker drugs flows from the reduced rates of transplant renal artery stenosis, a consequence of improved surgical techniques for this critical anastomosis. Recent data suggest that these agents may be

salutary in blocking chronic rejection [30, 31]. Indeed some have hypothesized that the hypertension, a consequence of the cytokine TGFβ, is related in part to activation of the promoter sequences of the gene for angiotensin generation with the fibrotic tendency and hypertension prevented by blocking the effect of angiotensin at its receptor. On the other hand, since the administration of angiotensin-converting enzyme (ACE) inhibitor agents could interfere with the autoregulation of the efferent arteriole, renal dysfunction might be seen with the use of these agents in cyclosporine-treated patients. Close follow-up is necessary.

Since management of hypertension should track pathophysiologic mechanism, it is important to remember that causes of post-transplant hypertension existant in the pre-cyclosporine era still may be at play. Steroids have been important contributors to post-transplant hypertension, leading clinicians to decrease steroid dose, use alternate-day strategies, and driving investigation of steroid withdrawal via substitution of more potent immunosuppressive drugs [32]. When transplant renal artery stenosis can be shown to be critical with lumens narrowed to 70% and the cause of elevated renins, surgery or angioplasty can be considered [33, 34]. In rare instances when renin elevations of the native kidneys can be shown to be causal of post-transplant hypertension, native nephrectomy can control hypertension.

Cardiovascular Disease

Cardiovascular complications are the most common cause of death in renal transplant recipients after the first post-transplant year with an incidence ranging from 14% to 50%. It has been reported that cardiovascular causes accounted for 48% of all specified deaths in renal transplant patients compared to 25% due to infectious causes [35]. Although the death rate from infections decreased significantly over the years, the death rate from cardiovascular causes including myocardial infarction, cardiac arrest, cardiac failure and stroke did not change. Even if not fatal, these complications denote significant morbidity in this patient population. Risk factors for cardiovascular disease in transplant recipients include male gender, old age at the time of transplantation, history of smoking, hyperlipidemia, history of ischemic heart disease before transplantation, glucose intolerance and diabetes, hypertension, and the use of steroids. Among serum lipid levels, high-density lipoprotein cholesterol (HDL) is found to be an independent risk factor for ischemic heart disease [36]. In asymptomatic diabetic renal transplant candidates, 25 – 40% have been found to have significant coronary artery stenosis prior to transplantation [37]. Cardiovascular mortality remains high in diabetic renal transplant recipients. It has been demonstrated that revascularization of coronary stenoses improves cardiac morbidity and mortality in this patient population [38]. Coronary angiography is now recommended for Caucasian type I diabetic renal transplant candidates age 45 or older since they had 88% prevalence of one or more coronary artery stenoses > 50% [39].

Increased plasma concentrations of homocysteine, the product of demethylation of the essential amino acid methionine, has been shown to be an independent cardiovascular risk factor [40]. Plasma homocysteine concentrations were found significantly high in renal transplant recipients with a history of an atherosclerotic event, such as angina, myocardial infarction and cerebral infarction, compared with healthy control subjects [41]. It has been demonstrated that serum homocysteine

concentration can be decreased by folic acid treatment. Prospective studies are needed to see whether folate supplements will be able to decrease cardiovascular morbidity and mortality in renal transplant recipients.

It is well known that cardiovascular morbidity and mortality rates are high in end-stage renal disease (ESRD) patients. Thus, transplant candidates should have a careful cardiac evaluation in order to prevent post-transplant cardiovascular complications and our efforts should specifically focus on improving the lipid abnormalities.

Table 3. Causes for Hyperlipidemia in Transplant Recipients

– Obesity
– Genetic predisposition
– Immunosuppressive agents
– Antihypertensive medications
– Age and Male gender
– Diabetes Mellitus
– Insulin resistance
– Hyperinsulinemia
– Diet

Hyperlipidemia

Since the correlation between lipid levels and cardiovascular events are well established, hyperlipidemia is an important concern in solid organ transplant recipients. There is also emerging data linking elevated lipid levels to chronic rejection. Lipid abnormalities have been reported up to 60 – 80% in this patient population. Post-transplant lipid abnormalities include increases in both triglyceride and total cholesterol levels, as well as increases in serum low-density lipoprotein (LDL) cholesterol and apolipoprotein B levels. Normal, low, or slightly elevated HDL cholesterol levels have been previously reported [42]. Lipoprotein(a) levels are found to be normal in some patients and increased in the others. In contrast to other lipoproteins importantly affected by steroids and cyclosporine, the impact of immunosuppressive drugs on lipoprotein(a) is unknown. Among serum lipids, HDL was found to be the best predictor of ischemic heart disease in this patient population [36]. The incidence of hyperlipidemia is approximately 75% in renal transplant recipients. Age, male gender, diabetes, heavy proteinuria, antihypertensive medications (beta blockers and diuretics), weight gain, renal dysfunction due to chronic rejection, and immunosuppressive agents were all implicated in persistent lipid abnormalities of renal transplant recipients (Table 3). Insulin resistance and hyperinsulinemia due to steroids, diuretics and weight gain were shown to be associated with increased triglyceride concentrations. Numerous studies have shown that treatment with cyclosporine either alone or along with steroids increases the levels of total and LDL cholesterol, and triglycerides [43,44].

There are controversial reports on the long-term effects of hyperlipidemia on graft and patient survival in kidney transplant recipients. Despite significant differences in serum cholesterol and triglycerides, actuarial graft and patient survival were found to be similar in some studies [45]. However, an association between hyperlipidemia and chronic allograft rejection has been reported. It has also been shown that pravastatin, an HMG-CoA reductase inhibitor, reduced the incidence of severe acute rejection and coronary vasculopathy in heart transplant recipients [46] and in kidney transplant recipients [47].

A recent meta-analysis of studies that investigated the therapies to lower serum lipids in

renal transplant recipients showed that HMG-CoA reductase inhibitors such as lovastatin, pravastatin, simvastatin, and fluvastatin caused the greatest and most consistent reductions in cholesterol, triglyceride, and LDL levels [48]. Diet caused modest reductions in total cholesterol and LDL. There were few studies with fibric acid analogues such as gemfibrozil or clofibrate, which showed some benefit, but less than those caused by HMG-CoA reductase inhibition. The observation that the propensity of fibric acid analogues to cause rhabdomyolysis is increased in patients with renal disease in general and post-transplantion in particular has led to the recommendations to use these agents with caution. Furthermore, the report by Ballantyne and colleagues on renal failure and rhabdomyolysis in heart transplant recipients using lovastatin has caused concern [49]. Full dose, hydrophilic pravastatin has been used safely in 24 kidney transplant recipients [50] while titrated lower doses of other statins have also been used with modest effect and safety. Thus, when the patient has persistently high LDL cholesterol levels (LDL 160 mg/dL alone, or 130 mg/dL associated with either ≥ 2 risk factors or previous history of cardiovascular disease) despite weight reduction, low-fat diet and regular exercise, it has been recommended to start a low-dose HMG-CoA reductase inhibitor. Increasing the dose of HMG-CoA reductase inhibitor while monitoring patient symptoms and creatinine phosphokinase (CPK) or the routine use of pravastatin are general treatment strategies in this patient population. The reports of rhabdomyolysis in cyclosporine-treated transplant recipients showed that these patients received high doses (80 mg/day) and/or concomitant therapy with gemfibrozil or niacin [51]. There are not many clinical studies using nicotinic acid in transplant recipients mostly due to its side effects. Modification of dietary saturated fat alone on an outpatient basis does not lower serum total or LDL cholesterol levels among renal transplant recipients [52]. Keeping patients on the lowest steroid dose (≤ 10 mg daily) could also be beneficial. The results of the ongoing steroid withdrawal studies will provide more data that are definitive. Currently, the recommended initial therapies for hyperlipidemia (total cholesterol > 200 mg/dL and LDL cholesterol > 130 mg/dL on 2 readings) in transplant recipients are diet and HMG-CoA reductase inhibitors [51].

Metabolic Bone Disease

Metabolic bone disease, a bane of the patient with chronic renal failure, is not completely reversed despite successful renal transplantation. Some mechanisms driving bone disease in the patient with impaired kidney function are indeed ameliorated by the successful transplant, while others remain and new problems are introduced. Bone loss is a well-known complication in renal transplant recipients, and has been shown to start as early as 3 months after transplantation. Reduced bone mass affects the resistance of bone to mechanical loads. Fractures of spine, hip, and ribs due to bone disease in transplant recipients can be devastating. The fracture rate in renal transplant recipients was found to be 3 times higher than in dialysis patients [53]. Bone disease occurs in both males and females. Elderly post-menopausal female patients are particularly at high risk for severe bone loss. Several factors including corticosteroid use, chronic metabolic acidosis, duration of dialysis, and pre-existing secondary hyperparathyroidism and aluminum accumulation are involved in the pathogenesis of bone

disease after transplantation. Corticosteroids increase bone resorption by decreasing calcium absorption and increasing urinary calcium excretion. They also inhibit bone formation. Although not directly proven, avascular necrosis is felt to be associated with long-term steroid use causing collapse of the femoral or humeral heads. Several studies showed that the cumulative dose of steroids is the most important factor on the loss of bone mineral density [54 – 56]. As little as 7.5 mg/day prednisone can cause significant bone disease. Numerous studies demonstrated that trabecular bone – spine, hips, distal radius, ribs – is primarily affected [53, 57, 58].

High pretransplant parathyroid hormone levels have been shown to enhance the trabecular bone loss early after renal transplantation [59]. An association with functionally different alleles of the vitamin D receptor gene and bone turnover and the degree of recovery of the bone mass has also been reported. It has been shown that renal transplant recipients with well-functioning grafts have 10 – 15% less bone mass measured by dual-energy X-ray absorptiometry (DXA) than healthy controls [60].

Cross-sectional and longitudinal studies showed that in long-term survivors of renal transplantation ongoing demineralization process of the vertebral bone persist as long as patients receive steroids [57]. The decrease of bone mineral density within the first 2 post-transplant years was associated with higher prednisone doses [53]. Interestingly, bone mineral density stabilized on a significantly lower level without further deterioration even in patients up to 20 years after transplantation. Conflicting results about the role of cyclosporine alone in bone metabolism have been reported. Animal studies showed that cyclosporine induces a state of high-turnover osteopenia [61]. Cyclosporine inhibits the bone resorption as well as the osteoclastic differentiation [62, 63]. It has also been demonstrated that in transplant recipients given cyclosporine with steroids, lumbar bone mineral density decreases significantly while it increases in patients given cyclosporine alone [58]. Dumoulin et al. have showed that in long-term renal transplant recipients cyclosporine treatment had no significant effect on calcium regulating hormones such as serum parathyroid hormone, 1,25-$(OH)_2D$, and osteocalcin as well as calcium and phosphorus levels [64]. Interestingly, it has been demonstrated that despite a significant decrease in parathyroid hormone levels compared to pretranplant levels, some patients may continue to have fasting hypercalciuria and exaggerated renal calcium loss exceeding the absorbed calcium suggesting a renal “leak” of calcium [65]. This defect in renal calcium conservation along with the renal “leak” of phosphorus might be contributing to the stimulation of parathyroid hormone secretion and bone abnormalities after transplantation [66].

Although bone histomorphometry remains as the “gold standard” technique to assess the severity of bone disease, dual photon absorptiometry also provides accurate data in transplant recipients [67].

Calcium supplements, vitamin D metabolites, calcitonin, thiazide diuretics, anabolic steroids, and biphosphonates have been proposed to be used in patients on long-term corticosteroid therapy. Occasionally, patients with persistent hypercalcemia and hyperparathyroidism may require parathyroidectomy. Regular exercise to maintain bone mass, hormone replacement therapy in post-menopausal women, and cessation of smoking are some of the preventative measures recommended. Ongoing studies on steroid withdrawal will provide information about the benefits of cessation of steroids on bone disease in transplant patients.

Malignancy

Although the more common neoplasms that afflict man (lung, breast, prostate, and colon) are not increased in the immunosuppressed patients, others such as squamous cell neoplasms and those of the immune cells themselves are importantly increased. In a cohort of 274 patients from a single center who were followed up to 29 years, skin tumors were the most common, followed by lymphoma, renal, bladder, and bronchial carcinoma [68]. The cumulative risks of tumor development were 18.4% at 10 years and 49.6% at 20 years. The relative risk of developing skin cancer, but not other malignancies, increased from 6.6% at 5 years to 20% after > 15 years. The incidence of squamous cell carcinoma is higher than basal cell carcinomas in transplant patients and the cancers behave more aggressively. According to a recent report from European Dialysis and Transplant Association – European Renal Association (EDTA-ERA) registry, colon cancer was found to be increased particularly at 10 years or later after transplantation [69]. In addition, young female recipients had an increased incidence of malignancies of both the body of the uterus and the cervix. Compared to normal individuals, renal transplant recipients have an increased prevalence of leukoplakia, dysplasia and cancer of the lip. Exposure to the sun, age at the time of transplantation and smoking are found to be the major risk factors [70, 71]. Dermatologic surveillance is a very important part of long-term follow-up of transplant recipients. All organ transplant recipients should be warned against excessive sun exposure. Surgical excision of the suspicious lesions, cryosurgery, radiotherapy, topical 5-fluorouracil, and either reduction or cessation of immunosuppression for aggressive and metastatic skin cancers are the treatment options.

An updated report on lymphomas by Dr. Israel Penn from the Cincinnati Transplant Tumor registry showed that lymphomas constituted 22% of all neoplasms occurred in transplant recipients, of which 94% were non-Hodgkin's lymphomas [72]. In 70% of cases, extranodal sites, mostly central nervous system, are involved. Surprisingly, when non-melanoma skin cancers and in situ carcinomas of the uterine cervix were excluded, Kaposi's sarcoma (KS), a rare tumor in general population, constituted 5.7% of neoplasms reported to Cincinnati Transplant Tumor registry [73]. KS is seen mainly in kidney transplant recipients with a much smaller incidence in other solid organ and bone marrow transplant recipients. The average time of appearance of KS is 21 months after transplantation. The majority of patients with KS reported were Arabic, African-American, Italian, Jewish, or Greek ancestry. When a transplant patient presents with reddish blue macules or plaques in skin or oropharyngeal mucosa, the diagnosis of KS should be considered and evaluated quickly because of the substantial mortality. The patient's human immunodeficiency virus (HIV) status should also be determined. Another entity, which is unique to transplant recipients, is posttransplantation lymphoproliferative disorder (PTLD). The incidence of PTLD varies among different organ transplants, ranging from 1 – 2.5% in renal to 9.4% in heart-lung transplants [74, 75]. The clinical presentation includes a benign infectious mononucleosis-like syndrome, extranodal tumor masses in the central nervous system or in the gastrointestinal system, and occasionally disseminated disease [76]. The risk of PTLD is high in patients with primary Epstein-Barr virus infection and in patients who receive antilymphocyte antibody preparations especially OKT3. PTLD is usually associated with a polyclonal or monoclonal B-cell prolifera-

tion. Assessment of clonality, expression of EBV-associated sequences or antigens, correlation of histological and immunophenotypical data are necessary to establish the diagnosis. Although there is no controlled trial with any of the treatment modalities, reduction or cessation of immunosuppression, surgical excision of the tumor, high-dose acyclovir or ganciclovir, interferon, chemotherapy, and radiation therapy have been reported for the treatment of KS and PTLD in kidney transplant recipients with some success. Another form of cancer in kidney transplant recipients is renal cell carcinoma. The overall prevalence of renal cell carcinoma of the native kidney was reported 3.9% in kidney transplant recipients [77]. Although no significant risk factor could be identified, the risk of renal cell cancer was approximately 100 times greater in a group of 129 kidney transplant recipients who underwent ultrasound examination of the native kidneys than in the general population.

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Pancreas-kidney Transplantation in Diabetic Uremic Patients: An Overview

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Introduction

The rationale for combined pancreas-kidney transplantation is based on the advantage derived from the simultaneous correction of hyperglycemia and uremia in diabetic uremic patients. In addition to the correction of these metabolic derangements, evidence suggests simultaneous pancreas-kidney transplantation (SPKT) may reverse some of the multisystem complications associated with long-term diabetes [56, 69, 168, 170]. However, pancreas-kidney transplantation has had a tumultuous evolution. The predisposition of the pancreas to vascular thrombosis, persistent problems with the management of exocrine secretions, and early problems with organ preservation, patient mortality, and graft loss hampered the widespread acceptance and application of the procedure prior to the early 1980s [13]. Early technical problems with the combined procedure also increased patient morbidity beyond that of diabetic uremic patients undergoing kidney transplantation alone (KTA). Failure of the early reports to demonstrate significant added benefits with the SPKT procedure fostered skepticism regarding the role of combined transplantation in the rehabilitation of diabetic uremic patients. Fortunately, refinements in the surgical procedure have significantly reduced graft-related post-transplant complications while advancements in immunosuppressive management have greatly improved graft survival. In addition, improvement in quality of life in SPKT recipients has been documented and may be related to the posttransplant amelioration of secondary complications of diabetes.

Outcome Associated with Renal Replacement Therapy in Diabetic Patients

Diabetes mellitus (DM) is a world-wide health problem, with over 1 million people diagnosed with Type I (insulin-dependent) DM in the United States alone [35]. End-stage renal disease (ESRD), a major sequela of diabetes, occurs in 35 – 45% of all diabetics including those with Type I and Type II DM [49, 115]. SPKT is one of several available treatment options for diabetic uremic patients. Over two-thirds of the more than 10,000 pancreas transplant procedures reported since 1993 were SPK allografts with pancreas after kidney (PAK) and pancreas transplants alone (PTA) procedures accounting for the remain-

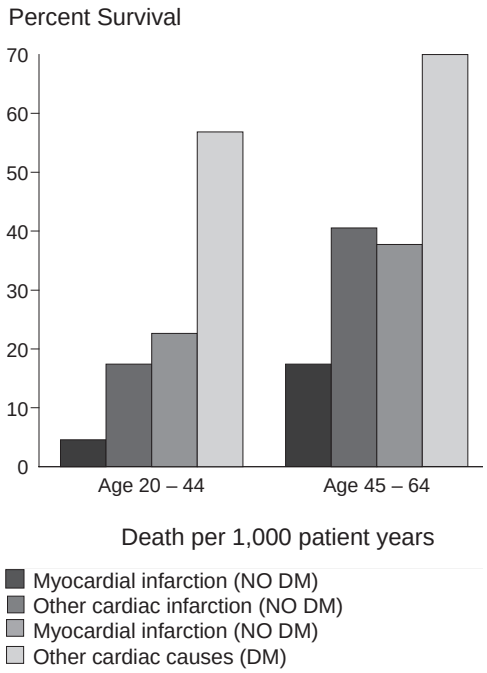

Figure 1. Death due to cardiac causes in uremic patients on hemodialysis.

ing one third [66]. Of all the pancreas transplants performed worldwide, two-thirds are performed in the United States [170] with approximately 1886 diabetic patients awaiting SPKT (United Network for Organ Sharing).

United State Renal Data System (USRDS) [173] data reveal an overall improvement in patient survival among all ESRD patients. However, the degree of improvement varies with primary diagnosis, patient age, gender, race, and treatment modality. Specific subgroups of the ESRD population, such as diabetic patients, continue to experience poorer outcomes. Diabetic uremic patients who undergo chronic dialysis experience substantially lower survival rates than non-diabetic uremic patients treated with dialysis [18, 31, 100, 173]. Diabetic uremic patients undergoing dialysis have a 1-year survival rate of 73% compared with survival rates of 78%, 82%, and 76% for patients with ESRD secondary to hypertension, glomerulonephritis, and all other causes, respectively dialysis [173]. Even more alarming is the 5-year survival statistic of 17% that occurs for diabetic dialysis-treated patients compared with 37%, 30%, and 33% for ESRD patients with a primary diagnosis of hypertension, glomerulonephritis, and all other causes, respectively [173].

In general, the death rate for diabetic hemodialysis treated patients is 1.3 – 2.7 higher for most causes when compared to non-diabetic age cohorts, with cardiac-related deaths significantly higher among the diabetic group (Figure 1). Between the ages of 20 – 44 years, deaths due to acute myocardial infarction occur at a rate of 4.2 per 1,000 patient years for non-diabetic uremic patients compared with a rate of 22.7 per 1,000 patient years for diabetic uremic patients. Similar discrepancies occur in the 45 – 64 year cohort with death rates of 17.4 and 37.7 per 1,000 patient years for non-diabetic and diabetic hemodialysis-treated patients, respectively. Other cardiac-related disorders account for death rates of 56.5 and 17.2 per 1,000 patient years in diabetic compared with non-diabetic hemodialysis-treated patients between 20 – 44 years of age, while rates of 70 and 40.5 per 1,000 patient years occur in diabetic and non-diabetic hemodialysis-treated patients 45 – 64 years of age. Like hemodialysis-treated diabetic patients, peritoneal dialysis-treated diabetic patients experience greater overall mortality and greater cardiac mortality than non-diabetic patients receiving similar replacement therapy. The cardiac-related death rates for peritoneal dialysis (PD) patients between 20 – 64 years of age are somewhat greater than the rates reported for hemodialysis (HD) patients of the same age cohort. Deaths due to acute myocardial infarction occur at an over-

all rate of 21.9 per 1,000 patient years for non-diabetic uremic patients compared with a rate of 43.9 per 1,000 patient years for diabetic PD patients. Other cardiac-related disorders account for death rates of 92.6 and 51.6 per 1,000 patient years in diabetic compared with nondiabetic PD patients between 20 – 64 years of age [173].

Treatment selection is known to influence the outcomes of diabetic uremic patients with better outcomes reported with kidney transplantation followed by PD and HD [101, 111]. These improved outcomes are particularly important in light of early concerns that diabetic uremic patients were not appropriate candidates for renal transplantation. The work of Najarian, Sutherland, and associates [110] at the University of Minnesota demonstrated, however, similar short-term success rates for both diabetic and non-diabetic patients undergoing KTA. This early work resulted in the widespread acceptance of KTA as the treatment of choice for diabetic uremic patients despite the propensity for post-transplant complications and the likelihood of recurrent nephropathy in the transplanted kidney. Concerns regarding recurrent nephropathy and post-transplant complications in diabetic uremic patients were gradually dispelled when it became clear that diabetic KTA recipient outcomes were substantially better than those of chronic dialysis-treated patients, that clinically significant nephropathy does not recur for several years post-transplant, and that diabetic kidney recipients experience similar short-term patient and graft outcomes to those seen in organ recipients who develop ESRD secondary to glomerulonephritis [11, 105, 169]. It is important to acknowledge that differences in patient outcomes related to transplantation and dialysis may be, in part, the result of differences in patient characteristics [173] and pretransplant selection [63]. It is probable that selection of diabetics with the lowest surgical risk for transplantation may bias outcome comparisons. Despite the potential selection bias, diabetics on the waiting list continue to have a higher mortality rate than diabetics undergoing transplantation, indicating that treatment-related factors significantly influence patient survival and morbidity [127].

Indications for SPKT

The relationship between improved glycemic control and the reduction of diabetic secondary complications was documented by the Diabetes Control and Complications Trials (DCCT) [29]. To date, pancreas transplantation remains the only procedure that is associated with *persistent* normoglycemia. Unlike intensive insulin therapy, pancreas transplantation is not associated with the risk of severe hypoglycemia or the dietary and lifestyle restrictions imposed by the diabetic state. SPK transplantation offers the added benefit of relatively normal renal function, thus eliminating dependence on both insulin and dialysis [132] and contributing to improved quality of life. While only 44% of patients in the DCCT [29] achieved normal glycosylated hemoglobin (HbA1c) levels *once* during the study, and < 5% sustained normal HbA1c levels, *all* of our SPKT patients have normal HbA1c levels and are persistently normoglycemic after transplantation.

With the increased availability of transplantation as a treatment option for diabetic uremic patients, it is crucial that careful consideration be given to patient selection. The main purpose of pancreas transplantation in the improvement of quality of life with prevention of the secondary complications of DM [35] and thus, patients with impending or established ESRD between 20 – 50 years of age particularly those with potentially reversible

diabetic complications are the best candidates for this procedure [151, 171]. Within this group of patients, life-long immunosuppression is an accepted risk given their need for kidney transplantation. However, the potential complications related to the addition of a pancreas should be examined in light of the potential benefits provided by the reversal of the diabetic state. Earlier referral and more careful patient selection should minimize concerns related to pancreas transplant-related patient morbidity.

Relationship between Timing of SPK Transplantation and Long-term Outcomes

The timing of transplantation is a critical issue for the diabetic patient with end stage nephropathy since rapid deterioration in autonomic gastric and cardiac function accelerates with the onset of ESRD, and preexisting diabetic macroangiopathy worsens with long-term dialysis [155]. Such significant diabetic sequalae may increase the risks associated with the transplant procedure or may eliminate the patient as a candidate for transplantation. Unfortunately, no clear criteria exist that delineate the "critical" period during which transplantation should occur to optimize outcomes. However, published data appear to support preemptive transplantation prior to the occurrence of significant deterioration in secondary complications and the onset of chronic dialysis [171]. Stratta et al. [162] reported comparable surgical outcomes in dialysis-dependent diabetic uremic patients receiving SPKT and diabetic uremic patients undergoing preemptive SPKT. Dialysis-dependent and non-dialysis patients attained similar patient (97% vs. 95%), kidney (95% vs. 91%) and pancreas (90% vs. 93%) survival rates. Aside from the potential cost savings, preemptive transplantation eliminates the complications and costs associated with long-term dialysis and has the potential to minimize the progression of secondary complications of diabetes.

Results of SPKT

Patient and Graft Survival

Both graft and patient survival post SPKT have improved dramatically over the last three decades with a one-year patient survival rate of 94% and graft survival approaching 85% [66]. Data also indicate that patient and graft survival are improved with SPKT when compared with pancreas after kidney (PAK) and pancreas transplant alone (PTA) with one-year graft survival rates of 83%, 71%, and 64%, respectively [66]. The introduction of FK506 (Tacrolimus) has lead to measurable improvements in graft success rates that exceed those reported with cyclosporine [64]. Recent reports of single center experience indicates that the one-year graft success rate for SPK allografts is approaching 90% [156].

Long-term Success Rates

With the improving short-term success of pancreas transplant, studies of long-term outcome are beginning to appear. The general trend in these studies is an observation that patient and graft survival rates remain stable after the second post-transplant year [156]. In addition, recent data confirmed that a lifetime of insulin independence after pancreas transplantation is possible because of a low rate of chronic rejection [112]. A recent report by Bruce et al. indicated that the 5-year actuarial patient, kidney and pancreas survival rates are 94%, 85%, and 86% respectively and that

estimated kidney and pancreas graft half-lives are 15 ± 2 and 23 ± 7 years respectively [16]. These data were generated using patients undergoing portal enteric pancreas transplantation. In a similar analysis, Stratta reported 10-year actuarial patient, kidney and pancreas graft survival rates of 93%, 82%, and 79% respectively in patient receiving systemic-bladder pancreas transplantation [164].

Most importantly, data from Wisconsin reporting on the follow-up of over 500 consecutive SPK transplants demonstrated not only excellent 10-year actuarial patient, kidney and pancreas graft survival rates (76%, 67%, and 67%), but also that kidney success rates at 10 years for the simultaneous procedure exceeded those for all other types of kidney transplants with the exception of HLA identical living related kidneys [156].

Long-term Pancreas Function

Several studies including our own [57] have previously demonstrated that short-term metabolic control is normalized by pancreas transplantation. A number of recent reports have analyzed long-term metabolic control and documented that successful pancreas transplant recipients are capable of maintaining normoglycemic and normal glycosolated hemoglobin levels for periods > 10 years after transplantation [13, 177], thus confirming that the risk of chronic rejection of pancreas transplants and gradual loss of function is equivalent to other organ transplants [102, 112]. That long-term freedom from diabetes may contribute to overall patient outcomes has been demonstrated in reports that 8-year patient survival after SPKT was better than a cohort of diabetic patients receiving kidney alone transplants [175]. This data was again reviewed at the 10-year mark and the SPK patients were confirmed to have a large survival advantage [178]. Although this outcome data is not randomized and is thus subject to selection and other bias, it still strongly suggests the SPK and the correction of continuous hyperglycemia are beneficial to the uremic diabetic.

Patient Selection and Transplant Management

Pre-transplant Evaluation

Recipients selected for SPKT should be free of significant cardiovascular co-morbid illness in order to withstand the surgical and post-surgical stress. The medical evaluation is tailored to the individual based upon the investigation of specific signs or symptoms [159]. The workup confirms the diagnosis of Type I DM, determines the patient's operative risk, establishes the absence of any exclusion criteria, and documents end-organ complications for future tracking following SPKT. In a suitable candidate, the evaluation is also used to determine the type and timing of the SPKT procedure [163]. At most centers, the major contraindication to SPKT is significant uncorrectable cardiovascular disease. However, in a recent study from the University of Maryland analyzing 316 IDDM patients being evaluated for pancreas transplantation over a 4.5 year period, only 4 (1.3%) exhibited absolute cardiac contraindications to transplantation [142]. Other relative contraindications include severe vascular disease, psychiatric illness, advanced autonomic neuropathy, and obesity.

Patients with Type I DM and impending or established ESRD who are between the ages of 20 and 50 years are considered optimal candidates for SPKT. Although some centers regard a history of blindness, major amputa-

tion, stroke, heart disease or active smoking as relative contraindications to transplantation [154], our experience indicates that with careful evaluations and intervention, some of these patient can be safely transplanted. On the other hand, age > 60 years, ejection fraction < 30%, and severe obesity (> 150% ideal body weight) are usually viewed as contraindications. Other contraindications, that are applicable to all solid organ transplant recipients, include the presence of active infection or recent malignancy, active substance abuse or dependence, recent history of noncompliance, or psychiatric illness.

The exact timing of SPKT relative to the degree of nephropathy deserves further discussion [160]. Many Type I DM patients with impending or projected renal failure are referred for transplantation before the initiation of dialysis [88, 136]. The rationale is to take advantage of the reputed benefits of transplantation over dialysis including improved survival, reduced costs, facilitated rehabilitation, diminished morbidity and arrest of the rapid progression of diabetic complications that occur in end-stage uremia. The timing of SPKT has to be considered, however, in view of increasing waiting times for all ESRD patients, the variable progressive nature of diabetic complications, and the diminished survival that IDDM patients have on dialysis. In general, we attempt to evaluate uraemic diabetic patients for the SPK procedure when the creatinine clearance is at 30 mL/m^2/min. This allows enough time for completing the evaluation and listing of patients prior to onset of dialysis. Listing of patients is usually accomplished when the patients have a clearance around 20 – 25 mL/m^2/min except if they have significant uremic symptoms requiring immediate listing.

In patients with established diabetic nephropathy, the choice between SPKT or pancreas after kidney transplantation can be problematic, particularly if there is a living donor willing to donate a kidney [157]. Historically, living-related donor kidney transplants in diabetic recipients are associated with an early survival advantage compared with cadaver donor kidney transplants [5, 22]. The somewhat increased morbidity of SPK and the desire to avoid dialysis, shorten waiting time and avoid depletion of the cadaver donor pool, has led to a reluctance of some centers to recommend SPKT to appropriate candidates with living donors. On the other hand, although consistently improving, the pancreas survival results of pancreas after kidney transplants are still somewhat lower than SPKT [66]. Based on these data, some patients with a suitable living donor may elect to receive a cadaver donor SPKT in spite of the increased risks associated with the procedure. In general, diabetic patients with an HLA-identical living donor should receive the HLA-identical kidney, in view of the excellent long-term patient and graft survival rates associated with these transplants [172]. The results of haploidentical or living non-related transplantation are comparable to the kidney results in SPKT, and the decision should be based on patient preference and projected waiting time, availability of cadaveric kidney and reimbursement issues [157, 163]. In rare cases, living donor segmental pancreas and kidney transplantation have been performed successfully either simultaneously or sequentially from the same donor [65]. Finally, if the patient is an acceptable candidate for a pancreas transplant and has no living donor available, then SPKT should be considered as primary treatment to establish insulin-independence and provide renal replacement therapy. Due to excessive cadaveric SPKT waiting times, however, some patients may be dually listed either for SPKT or kidney alone transplant, particularly to take advantage of zero-antigen mismatch kidney sharing [22, 172].

Donor Selection and Management

Donor selection and organ procurement are of paramount importance to the success of the SPKT procedure. Most brain-dead heart-beating donors that are appropriate for kidney, heart, lung, and liver donation are also suitable for pancreas donation. Although there is some evidence that donor hyperglycemia may have a deleterious effect on allograft function, the presence of hyperglycemia or hyperamylasemia per se are not usual contraindications to pancreas donation [5, 79].

In general, ideal pancreas donors range in age from 10 to 45 years and range in weight from 30 to 80 kg. Management of the multiple organ donor includes aggressive resuscitation to maintain hemodynamic stability, organ perfusion, and oxygenation. Resuscitative efforts usually result in significant hyperglycemia and intensive control with insulin may have a favorable effect on initial allograft function and survival. Liberal use of intravenous colloids and mannitol is recommended to minimize pancreatic edema. Judicious administration of vasopressors such as dopamine are indicated to maintain a systolic blood pressure > 90 mm Hg and promote diuresis. High-dose pressors and other agents that impact the splanchnic circulation and pancreatic perfusion should be avoided if possible to avoid ischemic hypoperfusion and the possibility of post re-implantation pancreatitis [61].

Organ Procurement, Preservation, and Preparation

Advances in organ retrieval and preservation technology have played an important role in the improving results of pancreas transplantation [152]. Combined liver, kidney, and whole-organ pancreaticoduodenal retrieval can be safely performed in virtually all donors irrespective of vascular anatomy [36]. At present, whole-organ pancreas retrieval is not compatible with small bowel procurement.

The introduction of University of Wisconsin (UW) solution into clinical transplantation has permitted safe and extended cold storage preservation of the pancreas up to 30 hours without compromise of graft function [152]. The enhanced margin of safety afforded by extended preservation in UW solution has increased the capability for distant organ procurement and sharing, minimized organ wastage, improved the efficiency of organ retrieval, permitted time for crossmatching and adequate preparation of the recipient, and has enabled semi-elective performance of the recipient operation. Moreover, the quality of preservation has improved, resulting in better initial graft function with fewer complications such as pancreatitis or vascular thrombosis [61].

Before the recipient operation, the pancreas is prepared for transplantation under cold storage conditions in UW solution. Bench reconstruction of the pancreas comprises several steps including oversaw of the duodenal loop, vascular reconstruction with iliac grafts to the splenic and superior mesenteric artery and adequate excision of retropancreatic tissue. The spleen is left attached to provide a "handle" during the transplant procedure as the vessels are reconstructed and the duodenal segment is prepared.

Surgical Techniques

Various techniques of pancreas transplantation are currently being used. Almost all employ transplantation of the whole organ with attached segment of duodenum extending from the first to the third portion of that organ. The drainage of pancreatic exocrine and duodenal section has been achieved with bladder

drainage [150], or with enteric drainage [54] with or without Roux-en-Y reconstruction [57]. Although the majority of procedures involve establishing venous outflow and thus insulin drainage to the iliac vein and systemic circulation respectively, our group has introduced a technique for portal enteric transplantation that has been associated with avoidance of hyperinsulinemia [54] and improvement of various metabolic parameters that are influenced by increased systemic insulin levels [7, 57, 84]. In addition, there appeared to be, in cyclosporine-imuran treated patients, an improved immunological benefit related to portal delivery of antigens with this technique [121]. In brief, the technique requires identification of a large tributary of the superior mesenteric vein to which the donor portal vein is anastomosed end to side. A Y-graft of the donor common iliac and bifurcation of external iliac and hypogastric arteries is attached to the superior mesenteric and splenic arteries of the pancreas. The donor common iliac is then passed through the small bowel mesentery and anastomosed to the recipient's common iliac in an end to side. Enteric drainage is performed by anastomosing the donor duodenum to a Roux-en-Y limb. This technique has been employed in over 100 cases at our institution and is increasingly used by other centers in SPKT [16, 66, 83, 165].

Postoperative Care

Caring for the SPKT patient in the early post-operative period requires thorough knowledge of the post-operative course of these patients and, in particular, the differences between them and diabetic patients receiving kidney only transplants.

Early recovery following SPKT is dependent on several factors including the development of post-operative diuresis, utilization of induction therapy, the development of post-operative pancreatitis or other surgical complications. Patients are generally cared for in the intensive care unit, require adequate monitoring of fluid and electrolyte balance, and cardiac parameters. Post-operative management emphasizes administration of non-glucose containing electrolyte solutions and administration of colloid, particularly in view of the low serum albumin levels seen in the early post-operative period. Nasogastric suction is continued for 48 – 72 hours and diet advancement should be slow due to pre-existing gastroparesis in these patients. Blood volume is corrected to maintain hematocrit > 28% to avoid postural hypotension. Peritoneal drains should be checked for amylase levels and removed only after amylase measurements return to levels similar to serum concentration.

Immunosuppression

According to registry data, rejection accounts for 32% of graft failures in the first year after pancreas transplantation [66]. Most centers performing pancreas transplants use quadruple drug immunosuppression with antilymphocyte induction because of a high incidence of rejection and general belief that the pancreas is an immunogenic organ. The introduction of new [147] immunosuppressants has led to an evolution of the management protocols aimed at increased efficacy of immunosuppression. Evolution of immunosuppression protocols at our center exemplifies this philosophy. Starting with quadruple immunosuppression with either OKT3 or ATGAM induction, plus cyclosporine, imuran and prednisone in the late 80's we have gradually changed to replacement of cyclosporine with FK506, imuran with mycophenolate mofetil (MMF) and elimination of induction

[166] or the utilization of the non-activating anti-CD25 [114] agents or thymoglobulin instead of OKT3 or ATGAM for high risk patients [58].

The calcineurin inhibitor, FK506 is started immediately post-transplant at a dose of 0.1 – 0.2 mg/kg orally in 2 divided doses, titrated to a 12 hour trough level of 15 – 20 ng/mL by IMX assay for the first 3 months. After 3 months time-averaged concentration (TAC) levels are maintained at 10 – 15 ng/mL. Oral MMF is begun immediately post-transplant at 2 – 3 g/day in 2 – 4 divided doses. The MMF dose is reduced in patients with gastrointestinal intolerance (nausea, vomiting, diarrhea) or when the total white blood cell count is < 3,000/mm^3. MMF is discontinued temporarily in patients with active cytomegalovirus (CMV) infection, septicemia, or when the total white blood cell count is < 2,000/mm^3. Corticosteroids are administered as intravenous methylprednisolone 500 – 1,000 mg intraoperatively followed by 250 mg on postoperative day one and then tapered to 30 mg/day oral prednisone by day 7 – 10. A gradual steroid taper is used aiming at an oral prednisone dose of 5 – 10 mg/day at one year. In pancreas alone recipients, the above triple therapy is employed in combination with 5 – 7 days of OKT3 or thymoglobulin induction. The first dose of the antilymphocyte agents is administered intraoperatively, with subsequent doses titrated to maintain CD3 counts < 10 – 50/mm^3.

Postoperative Monitoring and Diagnosis of Rejection

After transplantation, duplex ultrasonography of the pancreas and/or kidney is performed whenever clinically indicated. Recipients are serially monitored for daily fasting serum glucose, amylase, and lipase levels, renal profiles, cyclosporine or TAC levels, and complete blood cell counts. Metabolic control and hormonal profiles are assessed by intravenous glucose tolerance testing, fasting and stimulated C-peptide levels, lipid profiles, and HbA1c levels [43].

Rejection Following SPKT

Rejection is the most common cause of long-term graft loss [66, 170]. Unlike KTA recipients, SPKT recipients risk the likelihood of multiple organ rejection. Single organ rejection, particularly pancreas alone rejection has been reported but is rare [91]. Although there is relative agreement that rejection incidence judged by the accurance of kidney rejection is higher among SPKT recipients than patients with kidney transplant, this assertion is somewhat debatable [73]. Data from some centers indicate that SPKT and KTA recipients experience similar rates of kidney rejection (33% vs. 29%) [20], while others report greater rejection in the SPKT group [150, 168], with some centers reporting a 2 to 3-fold increase in acute rejection and greater likelihood of steroid-resistant rejection among SPKT recipients [132].

Kidney indices of rejection are known to precede pancreatic dysfunction in SPK recipients receiving both organs from the same donor [151, 170]. Although reversal of kidney rejection is usually associated with pancreatic graft rescue [170], isolated pancreas rejection is possible. When transplanted organs are from different cadaveric donors, kidney function is not a definitive marker of pancreas rejection. In bladder-drained pancreas transplants isolated kidney rejection is characterized by an increased serum creatinine without concomitant decrease in urine amylase while simultaneous rejection of both organs leads to an increase in serum creatinine and a

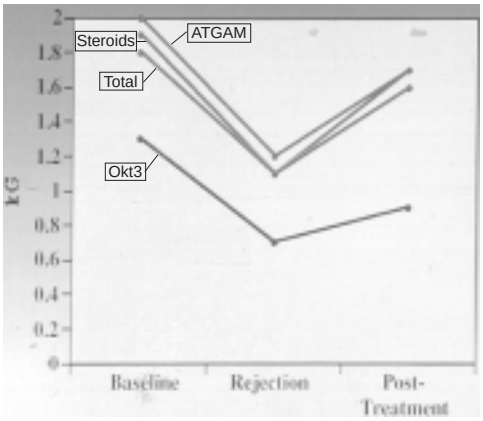

Figure 2. Response of Kg to anti-rejection therapy. Patients underwent IV glucose tolerance testing at various time points post-transplant. The slope of the decline of glucose tolerance curve (Kg) was measured and compared at point A (stable function), B (at time of rejection) and C (following anti-rejection treatment with steroids or antilymphocytes).

fall in urinary amylase [150]. Other signs of pancreas rejection such as elevation of serum lipase [167], amylase, pancreas graft tenderness and a decline in glucose tolerance have replaced urinary amylase as markers of pancreas rejection in non-bladder drained cases [122]. Utilization of fine needle aspiration cytology to screen for or confirm rejection has been described by Egidi [37]. Histological confirmation of rejection by pancreatic biopsy is usually the gold standard used to diagnose pancreatic rejection. We have described the first series of percutaneous pancreas allograft biopsies using real time sonography and confirmed its utility in the diagnosis of rejection [52]. We have also described the use of glucose disappearance rate (k_G), a marker of β-cell function, to predict pancreas rejection [40, 43]. Although the k_G value reflects first-and second-phase insulin response, it is largely dependent on first-phase insulin secretion. We found that changes in k_G differentiated rejection from non-rejection in the majority of patients. Decline in glucose tolerance was reproducible in stable patients, and returned to baseline after successful rejection therapy (Figure 2). In addition, the usefulness of a 20% reduction in k_G value was confirmed by percutaneous biopsy, which indicated pancreas rejection in over 82% of the cases [74]. In our study, the k_G value was more sensitive than urine amylase and serum anodal trypsinogen (SAT), and more specific than urine amylase levels in predicting rejection confirming that subtle changes in glucose hemostasis accompany pancreas rejection [74].

The severity of rejection is defined according to Banff criteria for kidney biopsies and by modification of the Maryland group classification of allograft rejection for pancreas biopsies. Mild renal allograft rejection is treated with intravenous methylprednisolone 500 – 1,000 mg/day for 3 doses. Anti-lymphocyte therapy for 7 – 10 days is used as the initial treatment for moderate or severe renal allograft rejection or for established pancreas allograft rejection. Steroid-resistant mild renal allograft rejection is also treated with anti-lymphocyte therapy.

Cytomegalovirus (CMV) Infection

CMV is a ubiquitous virus that affects transplant recipients. CMV infections are particularly important in the pancreas transplant recipients because of the large proportion of potential recipients that are CMV, negative and are thus at increased risk when transplanted with CMV-positive donor organs [42]. CMV infection is defined as a positive blood culture, antigenemia, or positive IgM titer. Invasive CMV infection is defined as symptomatic CMV infection or histologic evidence of tissue invasion. Treatment of CMV infection consists of intravenous ganciclovir for 2 – 4 weeks and a reduction in

immunosuppression. The use of newer markers such as CMV antigenemia assay [174] is being studied as a means for determining length of anti-CMV therapy. Oral ganciclovir is given for a variable period after treatment of documented CMV infection. Because of the immunosuppressive effects of a major CMV infection, other infections should be suspected and aggressively diagnosed in the patients with CMV. In addition, because ganciclovir is only virostatic and not viricidal [28] a suspicion of ganciclovir resistance should be considered in patients not responding to adequate treatment. Long-term anti-CMV prophylaxis should be continued in the small group of patients not developing antibody to CMV and remaining CMV IgG negative following a documented infection [42].

Complications

SPKT is associated with a higher morbidity than kidney transplantation alone in the uremic diabetic patient [161]. The transplantation of the pancreas involves an intra-abdominal operation, retroperitoneal dissection and anastomosis of non-sterile cavities such as the urinary bladder or bowel. These factors plus the extent of vascular anastomosis, the large number of smaller blood vessels on the surface of the pancreas and low blood flow to the pancreas itself predispose to the variety of surgical complications seen after pancreatic transplantation (Table 1).

The unique set of problems encountered by bladder-drained pancreas recipients has led to a steady rate of enteric conversion in these patients. Disconnecting the pancreas-urinary bladder anastomosis and reestablishing pancreatic exocrine drainage into the bowel is indicated for patients with refractory problems with dehydration, acidosis, urethritis or urinary tract infections. Collected series report enteric conversion rates of 10 – 20% and an operative complication rate of 10 – 20% with an enteric leak rate of about 6% [153].

Because of the potential of serious complications associated with vascular anastomosis and those related to enteric or bladder anastomotic leakage combined with the difficulty in reaching a firm diagnosis of suture line leakage, particularly in the enteric drained pancreas, early re-exploration of recipients where complications are suspected has been advocated. Besides confirming the diagnosis early, re-exploration allows efficient management of complications and rescue of the pancreas allograft. In general, the most common causes

Table 1. Surgical Complications After Pancreas Transplantation

Early Post Operative
– Prolonged ileus
– Prolonged gastroparesis
– Vascular thrombosis
– Intra-abdominal bleeding
– Suture line disruption
– Peripancreatic fluid collection
– Graft pancreatitis
– Lower gastrointestinal bleeding**
Delayed Complications
*Urologic Complications**
– Reflux pancreatitis
– Urinary tract infections
– Urethritis, cystitis
– Hematuria
*Acidosis, dehydration**
Duodenal loop obstruction
Recurrent pancreatitis
Delayed duodenal loop leaks

*More common and frequently more severe in bladder drained pancreas transplants
**Seen in patients with enteric drainage of the pancreas

for re-exploration following pancreas transplantation are vascular thrombosis, intra-abdominal bleeding and intra-abdominal infection. The incidence of re-exploration in most series varies from 20 – 30% [17, 38, 131]. Post-exploration, patients should be monitored carefully for the development of intraperitoneal and wound infections. This is also true for patients who have undergone a pancreatectomy who remain on continued immunosuppression for protection of a functional kidney allograft.

Late complications after SPKT have also been reported both in bladder-drained and enteric-drained transplants. Chronic bleeding and delayed perforations have been reported with a frequency of 3 – 5% in both types of transplants [42, 119]. Exploration and surgical repair has been associated with almost uniform graft salvage in these cases.

Impact of Successful SPKT in Diabetic Uremic Patients on Target Organ Complications

Neurological Dysfunction

Neuropathic dysfunction contributes to the development of foot ulcers [45], gastroparesis [81], impotence, diarrhea, orthostatic hypotension [45], and cardiac dysfunction including sudden cardiac death [71]. Coupled with the reduction in quality of life caused by these symptomatic neuropathies is the increased mortality that occurs in these patients, with 44% of the patients with symptomatic neuropathies dying within 3 years [181].

Diabetic Somatic Neuropathy

The observation that neuropathic complications occur with similar frequency in Types I and II DM, and secondary forms of diabetes (pancreatectomy, hemochromatosis) [125] has led to the belief that hyperglycemia is the pathogenic component of diabetic neuropathy. Furthermore, clinical observations from studies of diabetic patients associate poor blood glucose control with both early occurrence and severe manifestations of neuropathy [15, 125, 146]. These clinical observations are supported by evidence that changes in nerve conduction velocity are usually correlated with HbA1c levels [80]. The relationship is sensitive enough that transient improvements in HbA1c in response to intensive insulin therapy evoke improvement in nerve condition [124].

Although patients report consistent improvements in symptoms related to somatic neuropathies following SPKT, objective longitudinal data comparing SPKT and KTA recipients remains sparse. Overall the data seem to indicate that neuropathy improves following SPKT at levels exceeding those achieved in KTA recipients [25]. Our own data shows that improvement occurs at 12 months for both groups, while only the SPKT group experience continued improvement at 24 months post-transplant [120]. Other researchers [4, 95, 108, 143, 149] have reported similar improvements in symptoms and nerve conduction velocity following SPKT. In fact, almost a decade ago, the impact of pancreatic transplantation on somatic neuropathy in non-uremic patients had been reported by Kennedy et al. [89] who found a significant improvement in motor and sensory function in the pancreatic transplant patients.

Improvement in Autonomic Neuropathies

Initial studies examining autonomic functioning following pancreas-kidney transplantation were inconsistent, with some researchers reporting improvements in specific areas [118] while others reported no improvements [12, 46]. Inconsistent findings are probably related to the use of single measures of function in some studies, the variable status of patients at the time of transplantation, and the inclusion of clinically dissimilar patients in the control and experimental groups. Our results, which reflect multiple outcomes examined in a longitudinal fashion, indicate that SPKT patients experience greater post-transplant improvement in autonomic function than KTA recipients [69]. SPKT patients experienced significant improvements in multiple measures of autonomic function, specifically valsalva ratio, postural adjustment ratio, total pulse amplitude, and autonomic index, while KTA patients only experienced improvement in postural adjustment ratio [55, 69]. Gastric emptying was significantly improved in 52% of SPKT recipients compared with 42% of KTA recipients; in addition SPKT recipients experienced normalization of gastric cycle frequency with a marked decrease in symptoms that was not achieved in KTA recipients [51]. We and others [109], did not document improvements in solid gastric emptying, despite clinical improvement of patients' symptoms and improvement in liquid emptying following SPKT.

Of greatest relevance is the documentation that improvements in quality of life are related to objective improvements in autonomic function ratio [55, 69]. In addition, evidence supporting that restoration of autonomic control of heart rate variability and improvement in cardiac neuropathy is associated with a decreased incidence of sudden cardiac death has been produced by our group [71] and by others [116, 117]. The trend towards improved neurological functioning, even with the small samples reported in most series, suggests that future research will continue to confirm the clinical observation of superior improvement in both peripheral and autonomic neuropathies observed in SPKT recipients when compared to those receiving KTA.

Diabetic Nephropathy

Nephropathy is known to recur in diabetic kidney recipients [104]. The likelihood of the SPKT procedure jeopardizing renal allograft function, because of the high rates of rejection and the need for increased doses of nephrotoxic immunosuppression, has been advanced by some authors [137]. Biopsy data indicate, however, that unlike KTA recipients SPKT recipients did not experience glomerular basement membrane thickening [11]; it appears that the normoglycemia associated with pancreas transplantation prevented the progression of diabetic glomerulonephropathy [9]. Both our SPKT and KTA recipients demonstrate stable renal function for the first year following transplantation [39]. In longer follow-up SPKT recipients demonstrated greater preservation of renal function than KTA recipients at 24 months post-transplant despite significantly higher doses of nephrotoxic immunosuppressants and the increased rate of rejection experienced by the SPKT recipients. We also documented normal levels of urinary albumin excretion in the SPKT in contrast to the increased albumin excretion seen in the KTA patients [39]. Although Douzdjian reported lower renal function in SPKT recipients beyond the third year post transplant [33]. Other researchers have reported better or equivalent renal graft function in SPKT compared with KTA patients even when the kid-

ney for SPKT or KTA recipients were procured from the same donor [21, 27, 133]. As discussed earlier, a recent report of the Wisconsin experience indicated that the 10 year survival rates of the kidney in SPKT exceeded those of all other transplants with the exception of HLA identical living-related renal transplants [156].

Quality of Life

SPKT and diabetic KTA recipients experience significantly better quality of life than that experienced by pre-transplant pre-dialysis patients, pre-transplant dialysis patients, and SPKT recipients who have lost both grafts [123]. In general, SPKT recipients report the best quality of life with regard to satisfaction with physical activity, leisure time activities, and overall quality of life. However, SPKT recipients did not differ significantly from KTA recipients in these areas. Other researchers have also reported better quality of life, as measured by the Sickness Impact Profile, in transplant recipients compared with dialysis patients [44, 68].

We have found similar improvements in post-transplant quality of life using the Sickness Impact Profile, particularly in relation to improved post-transplant autonomic function [55, 69, 72]. Of particular note were the strong correlations ($R > 0.50$, $P < 0.05$) that occurred between improvements in gastrointestinal symptoms and 3 measures of functional ability reflecting quality of life [69]. Our findings demonstrate improvements in autonomic function and quality of life after SPKT that exceeded those experienced by KTA recipients. Other researchers also reported significant improvements in quality of life related to psychosocial functioning [144], reduced symptom severity [26], increased full-time employment, fewer hospitalizations, and fewer lost work days [113], and greater life satisfaction [185].

Because quality of life is an individually perceived phenomenon, the most valid method of assessment utilizes patients' pre-transplant measures as control data for comparison with their posttransplant measures. One inherent difficulty in assessing the difference in quality of life between patients receiving a SPKT and those receiving a KTA is the inability to establish equivalent pre-transplant control data for both groups. Coupled with this difficulty is the dilemma faced when attempting to compare 2 procedures that both markedly improve the patients' subjectively experienced quality of life. The most valid comparison of quality of life outcomes of the 2 procedures would therefore utilize individuals who have experienced *both* procedures and who, therefore, have the most knowledge regarding differences in quality of life associated with the procedures. In a recent study we compared quality of life patients who experience life as both a SPKT and KTA because of either pancreas graft loss or subsequent transplant of a pancreas (PAK). In this setting patients perceive significant differences in their quality of life as a SPKT vs. KTA recipient [72]. The most positive quality of life occurred during the life of their functioning pancreas allograft and was characterized by a sense of normality, freedom, and control that was not present during their KTA experience. This work represents the strongest direct evidence to date, of an additional impact of pancreas transplantation on the quality of life of uraemic diabetics treated by transplantation.

Diabetic Microangiopathy

Clinical data suggest that diabetic uremic SPKT recipients may require less frequent amputations and experience fewer foot ulcers

than KTA recipients [151]. However, no prospective studies have been published verifying this clinical observation and the data from some retrospective studies appeared conflicting [87, 92, 107]. As early as 1987, improvements in microangiopathy were observed in SPK allograft recipients [1]. In addition vascular reactivity transcutaneous muscle oxygenation, reduced reoxygenation times were observed in these patients. SPKT recipients have been shown to have improvements in capillary protein leakage, using fluorescin injections and computer technology [24]. Improvements observed following SPKT approximated that observed in normal subject. Our own work demonstrated significant improvement in reflex vasoconstriction in patients with SPKT beyond that seen in KTA recipients [50] confirming improvement in microcirculatory environment following reversal of diabetes.

Diabetic Retinopathy

Data from the DCCT [29] indicate that intensive insulin therapy can be associated with worsening of diabetic retinopathy for the first 2 years. After 3 years, intensive therapy was shown to delay the onset and slow the progression of diabetic retinopathy. The question of whether pancreas transplantation improves diabetic retinopathy has not been studied in a prospective randomized fashion. Early studies, however, indicated progression of retinopathy after pancreas transplantation [130] suggesting that advanced retinal disease is not reversible. Other data appear to dispute early findings and suggest that SPKT and KTA patients experience *stabilization* [8, 19, 141, 184] and in some instances *regression* of retinopathy [93, 183]. Wang et al. [183] found that 34% of SPKT recipients experienced regression in retinopathy while 25% of KTA recipients experienced regression. Only 22% of SPKT recipients experienced disease progression while 30% of KTA recipients experienced progression. Another report indicates that 2 patients with preproliferative disease experienced measurable bilateral *regression* in retinopathy [93]. One of the 2 patients with grade 3 to 4 retinopathy prior to SPKT was without evidence of retinopathy at 3 years post transplantation, further suggesting that retinopathy may be reversible in some patients. In general, more patients with SPK grafts (73%) experienced stabilization than a comparable group of KTA recipients (54%), 46% of whom experienced significant disease progression.

As previously noted, the majority of SPKT are performed in patients with advanced secondary complications such as ESRD or imminent uremia. Consequently, most of these patients have severe retinopathy, beyond the preproliferative phase, at the time of transplantation. Thus, these may not be the best patients to study because their retinal disease may be irreversible. As transplantation is undertaken earlier in the course of diabetic pathology, the relationship between retinopathy and the return of persistent euglycemia may become more clear. Preemptive transplantation, prior to significant retinal change, may result in very different long-term outcomes with regard to retinopathy [141].

Metabolic Control

Fasting and post-prandial euglycemia, normalization of glycosylated hemoglobin, and correction of hyperlipidemia and lipoprotein distribution occur following pancreas transplantation [13, 168]. Similarly, decreased total cholesterol [59, 97] cholesterol-high density cholesterol ratio [82], triglycerides, and increased high-density lipoprotein (HDL) levels [97] have been reported in SPK recipi-

ents. Post-transplant pancreatic function is known to ensure normal or near normal glucose metabolism for as long as 5 – 17 years post transplant in SPK recipients [112]. Studies of lipid profiles document that after SPKT significant reduction in very low-density lipoprotein (VLDL) particles was more pronounced than that seen in KTA patients [96]. Significant debate as to which fractions are improved still exists although there is general agreement that correction of diabetes improves lipoprotein fractions beyond that seen in uremic diabetic patients or kidney alone recipients but not to the level seen in non-diabetic patients [82, 96]. Hyperinsulinemia following pancreas transplant is thought to result from impaired insulin utilization, immunosuppressive therapy, and direct systemic delivery of insulin which eliminates hepatic degradation of the hormone. The exact impact of persistent hyperinsulinemia in SPKT patients is unknown, although peripheral hyperinsulinemia has the potential of accentuating hypertension and atherogenesis. These potential disadvantages have not materialized quickly following pancreas transplantation leading some to suggest that primary hyperinsulinemia in SPKT recipients, unlike the secondary hyperinsulinemia seen in obese non-diabetic patients and type II diabetics, does not result in hypertriglyceridemia and low HDL [34]. Recently, we and others have reported that placement of the pancreatic allograft with venous drainage into the portal circulation eliminates peripheral hyperinsulinemia while maintaining normal glucose metabolism. We have further demonstrated that portal venous drainage of the pancreas leads to greater improvements in the lipoprotein composition of Type I DM patients than does systemic venous drainage [84]. These finding of improved lipoprotein metabolism with portal delivery of insulin have been confirmed by Bagdade et al. [7].

Cardiovascular Dysfunction

Cardiovascular disease is the major cause of death in diabetic patients [20] who experience adverse cardiovascular abnormalities that include microcirculatory abnormalities, widespread vascular disease, and abnormal ventricular function [56]. The etiology of these functional changes are multi-factorial resulting from altered myosin ATPase activity and myosin isoenzyme distribution [30] and several hematological abnormalities which impair myocardial microcirculation and oxygenation (e.g. hyperviscosity, reduced erythrocyte flexibility, and increased HbA1c) [32, 106]. Left ventricular hypertrophy is present in 75% of patients on dialysis at the initiation of renal replacement therapy [67] and dysautonomia further contributes to left ventricular dysfunction as well as life-threatening dysrhythmias [50].

Studies examining the impact of SPKT on diabetic cardiomyopathy are just beginning. Despite general agreement that the correction of uremia improves cardiac function, it has been difficult to demonstrate a reduction in left ventricular hypertrophy following correction of uremia by KTA [85]. Until recently, the left ventricular dysfunction associated with diabetic heart disease was thought irreversible. However, animal studies indicate that insulin and oral hypoglycemic agents can reverse myocardial dysfunction [47, 126, 139] while islet transplantation improves systolic and diastolic function in diabetic rats [99]. Similarly, significant improvements in systolic function occur in newly diagnosed Type II diabetics managed by dietary reductions in blood glucose [182]. We have previously reported significant improvements in cardiovascular function following SPKT [56] and currently are investigating whether these improvement are long-term [53]. Our preliminary data suggests greater early (6 and 12-

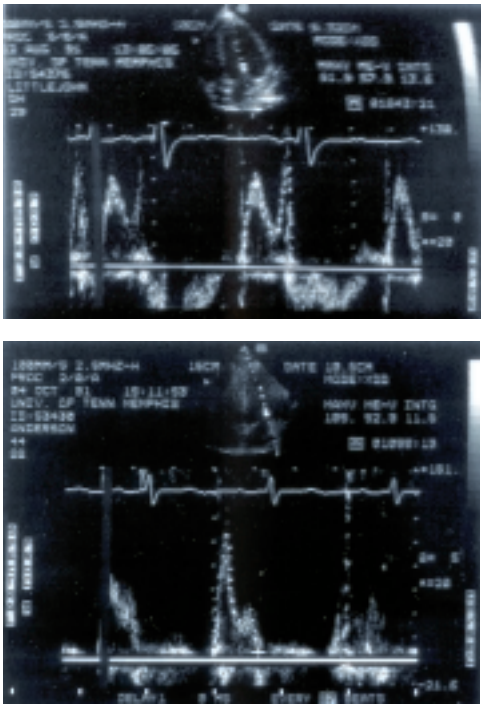

Figure 3. M mode echocardiography demonstrating abnormalities in diastolic function as indicated by abnormal atrial filling wave in diabetic uremic patient prior to transplantation (upper panel) and its correction following SPK transplantation with normalization of atrial filling (lower panel).

month) improvements in echocardiographic measures of systolic and diastolic function and left ventricular geometry in SPKT recipients compared to KTA recipients [56]. The SPKT group experienced restoration of normal systolic function, as evidenced by shortening fraction, at 6 months that continued at 12 months, with only 2 of the 22 patients (9%) demonstrating normal values pre-transplant in contrast to 13 of 20 patients (65%) post-transplant. Diastolic function also showed early and continued improvement (Figure 3) for the SPKT recipients as measured by early activation (E/A) ratios. E/A peak velocity ratio improved to near normal ratios at 6 months with improved function occurring for 14 of 19 patients (74%) at 12 months and normal ratios in 11 of 19 patients (58%). E/A integral ratios also improved for the SPK patients from pre-transplant to 6 and 12 months post-transplant.

Ventricular geometry also improved for the SPKT recipients who experienced a sustained decrease in posterior wall thickness, interventricular septal thickness, and ventricular mass. SPKT recipients more frequently experienced an improvement in interventricular thickness than did KTA recipients at 6 months (90% vs. 60%, $P \leq 0.04$) and at 12 months (85% vs. 50%, $P \leq 0.08$). Total ventricular mass also significantly improved in the SPKT group at both 6 and 12 months with total mass decreasing from 283.42 ± 11.20 grams to 198.52 ± 11.4 grams, $P \leq 0.0001$. Although the majority of KTA patients also experienced improvements in left ventricular mass, the degree of change was not statistically significant. These improvements persisted in the SPK recipients at 2-years post-transplantation while KTA recipients demonstrated stabilization [56].

Islet Transplantation: Future Prospects

Transplantation of pancreatic islets has several theoretic advantages over whole organ transplantation including the ability to cure diabetes without the need for complicated surgical procedures [90]. Because success of islet transplantation is still predicated on the utilization of immunosuppression [103], a large proportion of islet transplant recipients are also recipients of another solid organ transplant such as liver or kidney [6, 76, 179]. The continuous need for immunosuppression coupled with the poor results of clinical islet transplantation has led to general dismay regarding the procedure. Recent data, however, indicate clearly that long-term insulin inde-

pendence is possible following islet transplantation [3, 78, 140]. These results have ignited interest for novel approaches to make the procedure clinically successful.

Islet transplantation has also been shown to lead to dramatic improvements in metabolic control even in the absence of complete insulin independence [135]. Coupled with the results from the DCCT [29] demonstrating that maintenance of near normal glucose control can reduce or delay the onset of diabetic complications, these data have ignited interest in a wider utilization of islet transplantation. This shift in paradigm to islet transplantation from "cure" to "control" requires the development of methods that permit transplantation without long-term administration of immunosuppression [128, 129, 145].

Clinical Protocols and Results

Over the past several years the protocols for islet isolation have been standardized with most centers using modifications of the procedure described by Ricordi [134]. Recent reports indicate that with introduction of new enzyme mixes [98] in the isolation process islet yields have improved enough to allow single donor transplants [77]. In addition, it is now possible to select the isolation procedure with likelihood of best yield based on donor characteristics [138]. Isolation yields, however, are still dependent upon donor age, cold ischemic time and a variety of donor factors such as weight, and history of alcohol use. Following isolation and purification islets are counted using islet equivalents as a standardized measure of describing the isolation yield [6, 148]. Using this measure, that takes into account the three-dimensional structure of the islet, has been important in providing comparisons between different series and protocols for islet transplantation [14]. Islets are usually transplanted as soon as practically possible following isolation, although recent data demonstrate preservation of islet structure and function and good clinical results with islets maintained in culture for up to 30 days [48].

Following infusion of transplanted islets, tight control of blood glucose is maintained by exogeneous insulin until evidence of function of transplanted islets is detected, usually 7 – 14 days following the transplant. To promote islet engraftment, peritransplant administration of antilymphocyte globulin (ALG) is also used [75]. Immunosuppression is achieved by high-dose cyclosporine in most protocols and cyclosporine blood levels are monitored closely to maintain non-toxic ranges while avoiding rejection (levels between 300 – 400 ng/mL) [10, 75].

The islet transplant registry results continue to demonstrate gradual improvement of success rates over the past several years [76]. Primary non-function and rejection account for almost all graft losses in about equal proportion. Currently ongoing trails of tolerance induction in islet recipients provide hope for improved future application of this technology in uremic diabetic patients.

Conclusion

Successful SPKT renders patients euglycemic and eliminates the need for chronic dialysis therapy. Although there is no definitive data indicating that the addition of a pancreas to KTA recipients provides a survival advantage, the data clearly demonstrates that patients with both uremia and diabetes benefit from combined transplantation. Despite the limited numbers of patients available for comparative analyses, and the variable and late

entry of uremic diabetics into the transplantation pool, evidence suggests a trend towards amelioration of the secondary complications of diabetes following SPKT. The most compelling findings are the reported improvements in capillary function, cardiac dysautonomia, and diabetic cardiomyopathy that occur following successful SPKT. Verification of these results, along with recent developments in immunosuppressive therapy and the adoption of new portal enteric surgical techniques, may reveal the true potential of the SPKT procedure in the rehabilitation of uremic diabetics. Tremendous progress is ongoing in the area of treatment of diabetes by transplantation of human islets and new protocols are currently being introduced to make this a successful clinical option. Until this potential is realized, superior quality of life outcomes and freedom from the diabetic state will continue to provide justification for the procedure.

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Clinical Applicability of Xenotransplantation

Wayne W. Hancock

Introduction

Renal xenotransplantation, i.e. kidney transplantation between species, is not yet a clinical procedure. In fact, nor is xenotransplantation of any organ. However, it has happened in the past and may very well become important again, as discussed in this chapter. Thus, clinical renal xenografts were performed in the early 1960s, prior to the widespread development of dialysis programs and cadaveric organ transplantation, and at least in one small series were surprisingly successful. Moreover, an interest in xenografting of kidneys, and other organs has arisen again in recent years as donor supply has fallen increasingly short of the numbers of potential recipients.

In the U.S., as indicated in 1994 data from the United Network for Organ Sharing (UNOS), about 3,000 patients died awaiting an organ transplant, and a further 100,000 died without ever having "qualified" for a place on the respective waiting list, because of their age or other conditions (Figure 1). The trend in supply vs. demand is bleak. From 1988 – 94, the waiting list increased at a rate of 22% per year while the total number of transplants increased by only 8% per year. Using the 22% rate of increase yearly, the waiting list by the year 2000 will be ~60,000 patients, the bulk of which will be on renal transplant lists. Since UNOS estimates that < 50% of patients under 50 years who are on dialysis are placed on renal transplant waiting lists (27,498 for 1994), in part because their chance of finding a donor is considered bleak, and given there are at least 186,822 patients in the U.S. currently on dialysis, a demand for 100,000 organs for renal transplantation by the year 2000 is foreseen.

There are further reasons for development of clinical xenotransplantation. First, the donor may be engineered such that a xenograft may fulfill more functions than that of an allograft; e.g. a diabetic with renal failure might be given a renal xenograft in which insulin-producing β-cells were genetically engineered. Second, some conditions leading to organ failure can recur in an allo- but not in a xenograft. e.g. a liver xenograft is considered resistant to recurrence of hepatitis B or other hepatotrophic human viruses. Third, the xenograft can be obtained under optimal conditions, such that an ideal donor organ size, with minimal or no preservation injury, is likely.

Given these reasons in favor of xenotransplantation, the neophyte might reasonably ask "Why not?". This chapter deals with an explanation of the main limitations to xenotransplantation, including an outline of hyperacute rejection which can destroy a vascularized xenograft within minutes in arguably the most

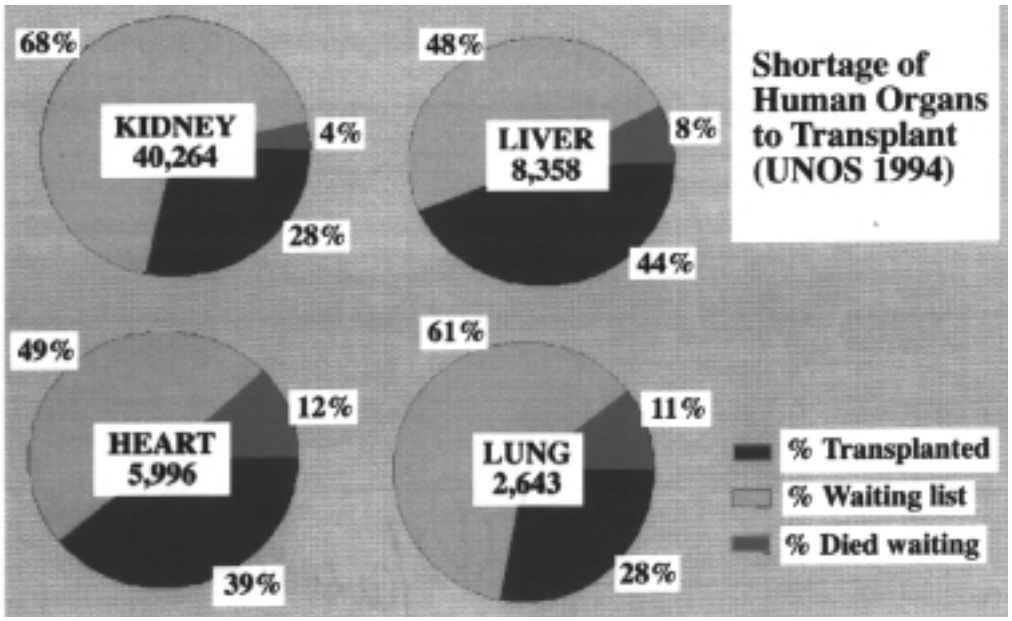

Figure 1. The impetus for the development of xenotransplantation as a clinical option is the shortage of allograft organ donors for transplantation. UNOS data (left) give the numbers of patients on waiting lists for organ transplants in the U.S., and show the breakdown as to those receiving a transplant vs. those still awaiting, or dying while awaiting, a transplant. These are conservative estimates of the numbers of patients whom would benefit from a transplant since only those accepted into transplant programs are shown. estimates by Roger Evans (Mayo Clinic) of the unmet need for organ allografts (right) indicate considerably greater numbers of transplants could be performed if organ supply was not the limiting factor.

violent immunologic response known. Thus, after a brief historical review, the principles, pathophysiology and barriers to vascularized organ xenografts are described, followed by considerations of infectious risks, biocompatibility issues and what will be required for the development of an infrastructure to support clinical xenotransplantation.

After reading this material, one should be conversant with the key pathogenetic mechanisms responsible for xenograft rejection; directions in research to overcome this problem; and a sense of where the field will head over the next 5 years, by which time many clinicians believe that clinical xenotransplantation will be under evaluation in trials in various transplant centers around the world.

History of Xenotransplantation

Scientific reports of xenotransplantation, or heterotransplantation as it was known until the 1970s, were first published over 90 years ago, and dealt particularly with renal grafts (reviewed in [18]). Princeteau, in 1905, placed slices of rabbit kidney in the nephrotomy of a child with renal failure and noted an immediate increase in urine output and cessation of vomiting, though the patient died of pulmonary complications on day 16. In 1906, Jaboulay tried xenografting with vascular anastomosis of a pig kidney, and in a second case, a goat kidney, into the antecubital space, but neither graft functioned, apparently due to vascular thrombosis. In 1910, Unger grafted

the kidneys of a non-human primate into a man with renal failure, but the patient died at 32 hours with venous thromboses. Neuhof, in 1923, transplanted the kidney of a lamb into a patient dying of mercury poisoning; the patient died 9 days later, apparently of non-renal causes. However, scientific interest declined in the 1920s, as it became clear that transplants were subject to a powerful immune response.

In the 1950s, as immunosuppressive drugs were developed and allografting between twins was shown to overcome renal failure and provide a good quality of life, interest in transplantation was renewed. However, problems with organ procurement and limited knowledge of organ preservation severely curtailed development of allograft programs. Reemtsma, Starzl and others began programs of experimental xenotransplantation using chimpanzees (or baboons, which gave far less satisfactory results) as donors; the chimpanzees were discarded from circuses or from the burgeoning space program of the time! A series of patients with terminal uremia and maintained on dialysis were offered the choice of supportive therapy; an allograft (living-related or cadaveric) if and when available; or a xenograft. The longest xenograft survival (still unrivaled) was in a patient who in 1963 received a chimpanzee renal graft and died, with normal renal function, of an unexplained intercurrent illness nine months later; soberingly, at post-mortem, histologic evidence of chronic rejection was noted.

At this time, a consensus was reached between the groups active in the field that, compared with the use of baboons or Rhesus monkeys, the chimpanzee was the best choice as a non-human primate donor. However, even in the 1960s, only minuscule numbers of chimpanzees were available for this purpose, and this situation became worse in later years as the chimpanzee was listed as an endangered species. By 1965, chronic dialysis and cadaveric transplantation became available, and in the absence of effective means to control xenograft rejection, all groups discontinued their clinical xenograft studies.

Choice of a Donor Species and Risk of Zoonoses

Given the restrictions on use of chimpanzees, other species have received attention as potential sources of organs for human xenotransplantation. Baboons are ~ 30 times as plentiful as chimpanzees, but, as with use of non-human primates generally, have major logistic and other limitations. None of these species does particularly well in captivity, all have long gestation times and few offspring, their use is expensive, leads to widespread objections on ethical and social grounds, and may be associated with risks of infections (zoonoses). A committee from the U.S. government's Food and Drug Administration (FDA), in hearings completed in July, 1995, evaluated the public health significance of clinical trials using xenogeneic tissues. Summaries and recommendations from these hearings, and further guidelines arising from the Public Health Service (PHS), await publication in the Federal Register. With the background of the human immunodefiency virus (HIV) epidemic and recent Ebola virus outbreaks, the government groups expressed concern over the potential for inadvertent transmission of infectious agents that would pose a threat to the recipient, health care workers, their contacts and, potentially, the general community. The agencies considered that primate donors pose the greatest risk for transmission of latent or intracellular organisms, including retroviruses.

Seeking an alternative, most investigators have agreed upon use of pigs as xenograft

Figure 2. Key considerations in the choice of a donor species for xenografting.

donors. Over 90 million pigs are raised and slaughtered in the USA each year. In contrast to non-human primates, pigs breed well in captivity, have large litters and their use raises few objections in the broad community. The FDA considered the use of pig tissues for xenotransplantation was less likely to introduce new pathogens to humans, given the close and prolonged contact of these species, than was the case if using primate donors. The PHS regulatory guidelines for xenotransplantation are expected to promote development of animal sources of donor organs which are free of zoonotic disease, place responsibility for ensuring the quality of donor tissues on the supplier, urge transplant teams to independently monitor the microbial status of donor tissues, and provide long-term follow-up of patients and their contacts for development of diseases of public health significance.

Concerns of disease transmission by a xenograft into a patient have led to recognition of a special case of zoonoses, termed xenoses [12]. Xenoses are of particular significance since the pathogen is placed deep inside an immunosuppressed individual. The large number of potential pathogens have vexed many investigators and led to attempts to identify disease-free herds of pigs, developed under gnotobiotic conditions, for clinical xenotransplantation. While federal guidelines for the development, screening and post-transplant monitoring of such clinical xenografts remain under development, the recent recognition that pig cells can harbor, and transmit to humans, pig retroviruses has been a particularly sobering event [27].

Concordant vs. Discordant Species Combinations

Use of pigs as xenograft donors, predictably, has its additional down-sides, the key one known to date being that pig xenografts elicit hyperacute rejection when transplanted into primate recipients. Calne suggested the use of the terms concordant and discordant to describe the relationship of various species with regard to xenografting, with the emphasis on the outcome following revascularization (Figure 2). Concordant combinations, including non-human primate to man, typically take several days to reject, whereas discordant combinations, such as pig to primate, are subject to a violent response and fulminant hyperacute rejection within minutes to a very few hours of transplantation.

Hyperacute Rejection

Xenoreactive Natural Antibodies

With the exception of a pig liver which was transplanted into a patient with end-stage liver failure [28], who survived < 24 hours, all relevant data involving pig xenografts has arisen so far from pig to non-human primate transplantation, plus from ex vivo perfusion or cell culture studies. The key point is that humans have preformed or so-called xenoreactive natural antibodies (XNA) directed against non-primate species. These XNA, which include IgM, IgG and probably IgA classes, appear to arise in early neonatal life following colonization of the large bowel by coliform bacteria. The majority of XNA recognize carbohydrate moieties associated with the bacterial cell wall and are polyreactive, binding many similar but non-identical residues.

Demonstration of the presence of XNA amongst humans, apes and Old World monkeys (catarrhines) but not other species, including New World monkeys (platyrrhines), provided the key to understanding the outcome of discordant xenografts involving humans or baboon recipients [15]. The majority, but not all, of human XNA are directed against a terminal carbohydrate of linear B-type, Galα1,3-Galβ1GlcNAc-R, where a galactosyl residue is linked to another galactosyl residue ("α-gal"), which in turn is linked to a N-acetyl-glucosaminyl residue; this process is controlled by a glucosidase not found in humans, called galactosyl transferase.

Attempts are underway to "knockout" expression of the α1,3 galactosyl transferase gene by pig cells as a strategy to markedly diminish pig organ immunogenicity following xenotransplantation. Antisense approaches have shown that this step largely abrogates the cytotoxicity of human serum to pig cells in vitro, and once development of a suitable pig stem cell line is achieved, targeting of this gene by homologous recombination is planned. However, initial studies indicated that targeted deletion of the gene in mice did not significantly affect the survival of mouse xenografts transplanted into non-human primate recipients [11]; apparently such mice showed a terminal N-acetyl-fucosamine epitope which is also recognized by human XNA, indicating that, as with much of xenotransplantation, unforeseen obstacles are present.

An alternate approach is the genetic modification of α-gal expression. By upregulating expression of H-transferase, an enzyme which competes for similar substrates as galactosyltransferase, in transgenic pigs the expression of α-gal-containing molecules may be reduced [8], though the efficacy of this procedure has yet to be tested rigorously in vivo. The combination of α-gal knockout and H-transferase express-ion may be more powerful than either alone. However, given that decreasing the immunogenicity of pig tissues for primate recipients by manipulation of the donor animal is of uncertain value, various groups have begun to consider downstream events and additional sites for therapeutic intervention. Features of discordant xenograft rejection are considered next, as well as strategies to interrupt various points of the primate immune response.

Pathobiology of Hyperacute Rejection

Antibodies and complement. Following revascularization of a pig → baboon xenograft, the classical features of hyperacute rejection are engorgement and discoloration of the or-

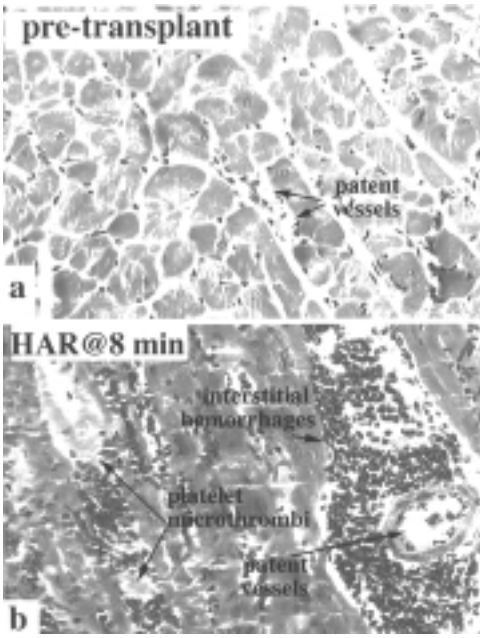

Figure 3. In contrast to (a) pre-transplant tissues which show normal morphology, (b) hyperacute rejection (HAR, 8 minutes post-transplant) of a pig → primate cardiac xenograft demonstrates interstitial hemorrhages and platelet microthrombi (arrows); in both groups, large vessels remain patent (Paraffin sections, hematoxylin & eosin).

gan, and by light microscopy, interstitial hemorrhages with platelet microthrombi (Figure 3). Immunohistologic analysis shows dense deposition of immunoglobulins and complement components throughout the vascular bed, consistent with the presence of host XNA directed against carbohydrate moieties on endothelial and other cells. Though early studies emphasized the predominance of IgM deposition, recent studies have established that deposition of IgG and IgA also occur [24]. This is important since the presence of IgA antibodies provides a mechanism for activation of the alternate pathway of complement. Indeed, several alternate pathway components, including properdin and Factor B, can be shown to co-localize with intragraft IgA during development of hyperacute rejection (Figure 4). Indeed, in rodent models such as the well-studied guinea pig → rat combination, alternate pathway activation, regardless of XNA deposition, is the key mechanism of hyperacute rejection [30].

Knowledge of the regulation of the complement system is central to an understanding of modern genetic approaches to control of hyperacute rejection (Figure 5, Table 1), and will be considered in the following sections. The presence of IgG can also provide a ready means for recruitment and activation of leukocytes bearing Fc receptors (CD16, CD32, CD64) in grafts which survive the initial post-transplant period.

Platelets. Though less studied than XNA and complement, hyperacute rejection involves activation and degranulation of platelets through multiple mechanisms, including local generation of complement fragments (C5b – C9); C3a and C5a-induced mast cell degranulation, histamine and serotonin release, and local generation of platelet-activating factor (PAF); FcR signaling upon exposure to deposited XNA; or ischemic injury and endothelial cell retraction with platelet GP1b interaction with subendothelial matrix-bound von Willebrand factor (vWF). Even in the absence of complement activation, there are multiple signals to stimulate platelets. An additional factor is the very rapid loss of endothelial ecto-ATP diphosphorylase (ecto-ATPDase) which normally maintains a non-thrombogenic state at the endothelial surface (Figure 6). Loss of ecto-ATPDase (CD39) expression occurs as a result of ischemia/reperfusion injury, complement activation and other signals [23, 33] (Figure 7). Though the extent of platelet microthrombi formation may not be enough to cause rapid graft dysfunction through purely physical disruption of blood perfusion through the microvasculature, platelet aggregation and acti-

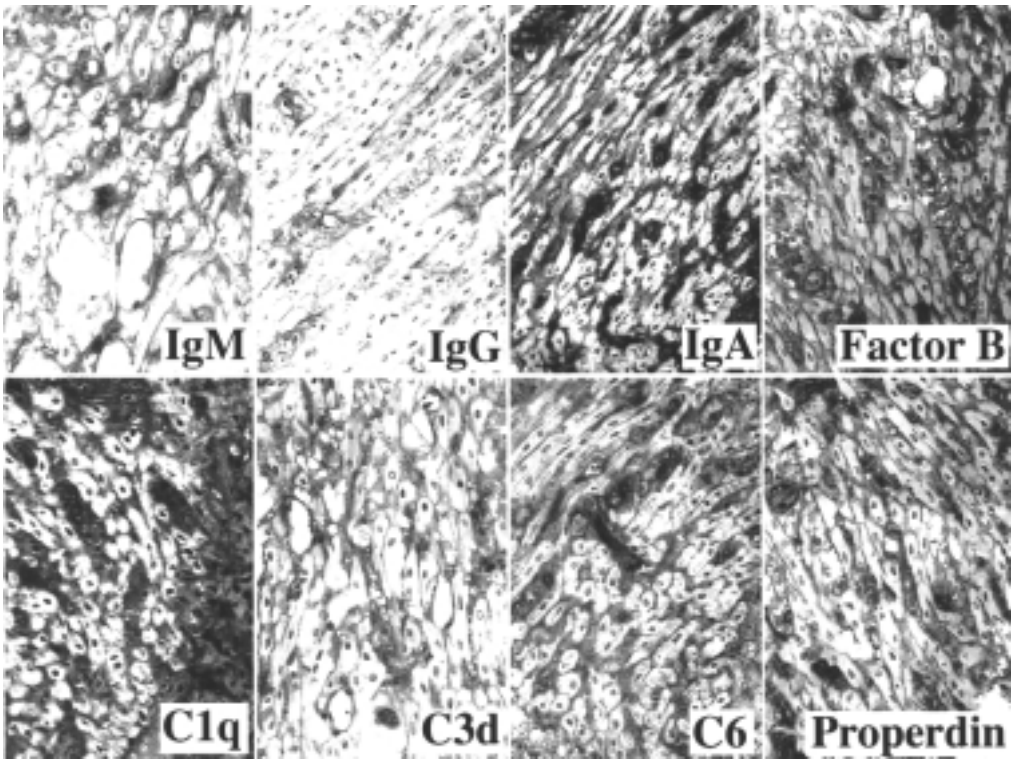

Figure 4. Hyperacute rejection of a pig-baboon cardiac xenograft is associated with dense endothelial deposition of IgM, IgG and IgA classes of XNA, leading to activation of both classical (C1q) and alternate (factor B, properdin) complement pathways. Both pathways activate C3 and lead to generation of the terminal pathway, as demonstrated here by endothelial localization of C6. See text for a discussion of the origin and nature of human XNA (Cryostat sections, immunoperoxidase).

Table 1. Human Regulators of Complement Activation (RCA Molecules)

RCA	Size	Membrane	Distribution	Actions
CD35 (CR1)	190-280 kD	Transmembrane	Blood cells except platelets	Decay-accelerating and cofactor activity
CD46 (MCP)	55-70 kD	Transmembrane	All except RBC	Cofactor for factor I-mediated cleavage of C3b, C4b
CD55 (DAF)	70 kD	GPI-linked	All cells	Inhibits C3 & C5 convertases, and enhances theirdissociation
CD59		18-20 kD	GPI-linked	All cells inhibits insertion of C8 and C9 into membraneattack complex

*The RCA listed (whose sites of action are shown in figure 5) are those being tested or currently used in experimental models and are likely to reach clinical usage; additional RCA which are not discussed include CD21 (CR2), C4bp and factor H.

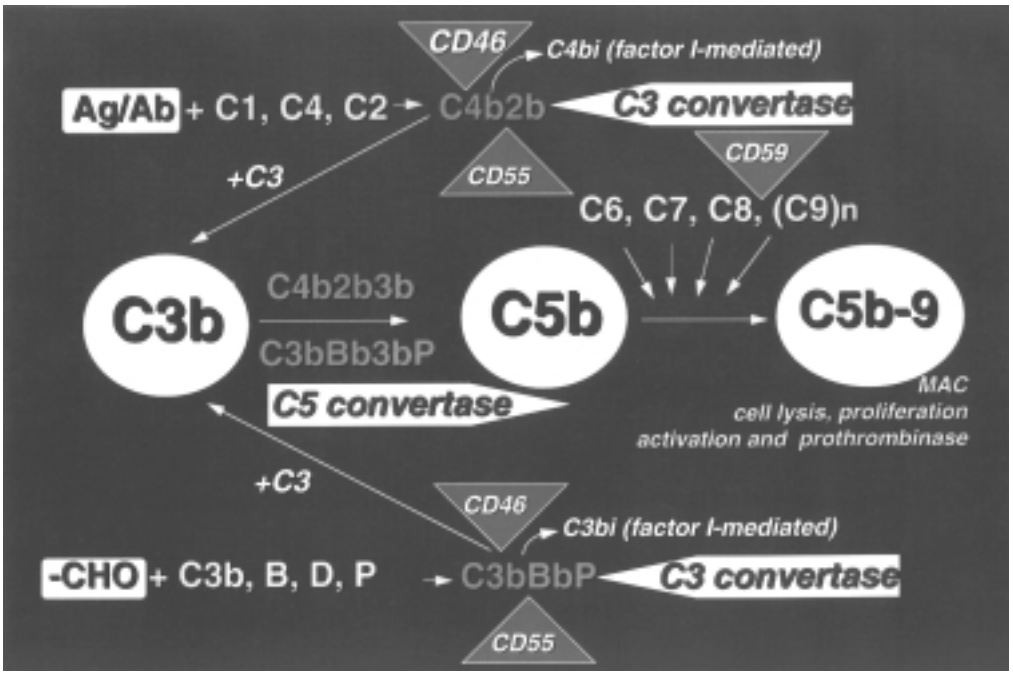

Figure 5. Dual routes for complement activation as a result of antigen binding by IgM or IgG (classical pathway), or carbohydrate (-CHO) or IgA activation of the alternate pathway. Each pathway has a respective C3 and C5 convertase. Events common to each pathway, from generation of C3b onwards, are shown only in the upper panel. Regulators of complement activation, whose properties are detailed in Table 1, are shown within red triangles; these RCA are of particular interest given these species-specificity and use in development of transgenic pigs in which high level expression results in abrogation of hyperacute rejection despite the deposition of XNA and early complement components.

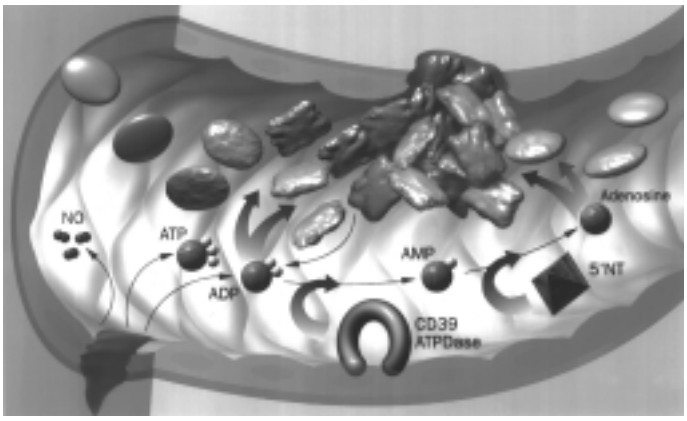

Figure 6. ATPDase (CD39) is an endothelial membrane-enzyme which by degrading ATP and ADP limits local platelet aggregation. Rapid loss of ATPDase during inflammatory events contributes to platelet aggregation and thrombosis.

vation lead to fibrin deposition. In addition, as detailed below, if hyperacute rejection is avoided, subsequent development of delayed xenograft rejection can be linked to platelet activation in the very early post-transplant period (Figure 8). Targeting of platelets with an anti-P-selectin antibody, PAF antagonist, or glycoprotein (GP) IIb/IIIa antagonist sig-

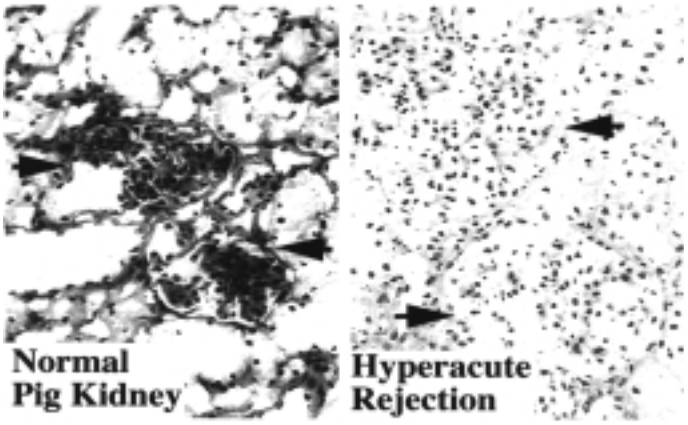

Figure 7. Enzyme histochemical demonstration of the loss of intrarenal glomerular and endothelial ATPDase activity as a result of local complement activation following pig-primate xenografting; such loss contributes to platelet deposition and hypoxia which characterize hyperacute rejection (Cryostat sections, hematoxylin).

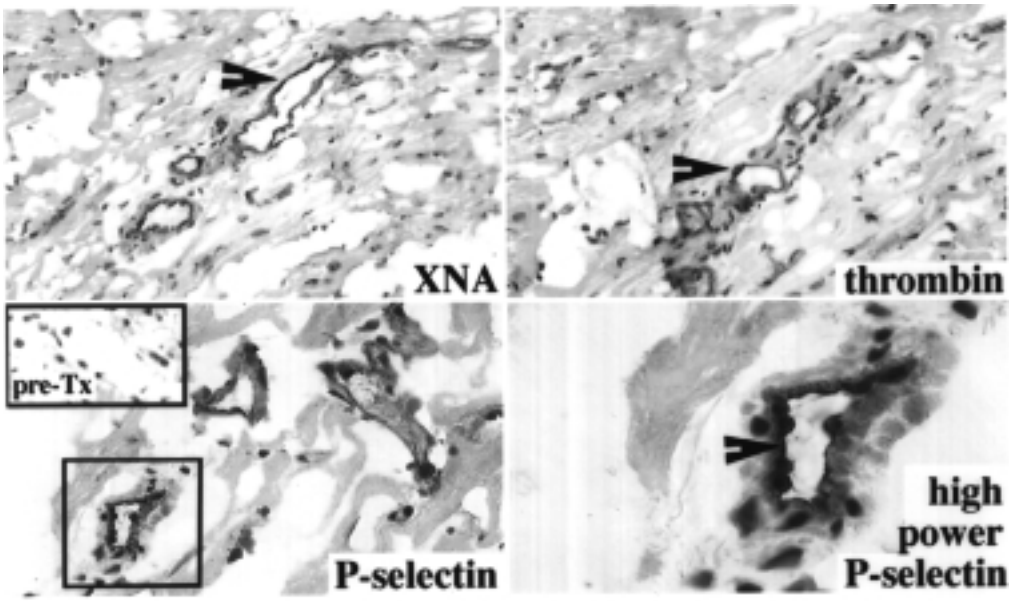

Figure 8. Within minutes of pig cardiac xenografting into a decomplemented primate recipient, XNA and thrombin are bind to donor endothelial cells, and P-selectin is translocated to the surface membrane where it can tether and activate host leukocytes. P-selectin exists in resting endothelial cells within Weibel-Palade bodies but the antibody used does not recognize this conformation (red box, lower left). The unfolded molecule is seen throughout the vasculature within minutes of engraftment and reperfusion, and one such vessel (black box) is seen at high power to demonstrate surface expression (arrow, lower right) (Cryostat sections, immunoperoxidase).

nificantly prolongs survival in some discordant models [7, 10].

Coagulation. Rapid assembly of coagulation factors on the platelet surface occurs through several related events. Receptors for factor V are upregulated upon platelet activation, and platelet membrane phospholipids are exposed as a result of microparticle formation, facilitating the binding and assembly of a prothrombinase complex. Platelets also degranulate, resulting in high local concentrations of fibrinogen and other coagulation fac-

tors present in alpha granules. Lastly, the trigger to platelet aggregation provided by thrombin or collagen results in release of ADP and serotonin. The combined effects of local platelet aggregation and activation are activation of coagulation and dense fibrin deposition, causing graft ischemia and rapid, progressive loss of organ function. A key role for coagulation, as powerful as that of complement, can be demonstrated in ex vivo perfusion systems [32].

Type I endothelial activation. Knowledge of endothelial responses during hyperacute rejection is very limited, whereas considerably more is known of the effects of XNA, complement and thrombin on cultured endothelial cells. Endothelial responses during hyperacute rejection do not involve gene activation or protein synthesis, and are therefore examples of what some term as type I endothelial activation. Within minutes of re-vascularization, P-selectin is translocated from cytoplasmic Weibel-Palade bodies to the membrane surface (Figure 8), where it persists for several hours (compared to in vitro studies wherein P-selectin expression typically lasts only minutes). P-selectin upregulation in vivo can occur as a result of endothelial cell stimulation by thrombin, histamine or the membrane attack complex of complement (C5b – 9). Additional events include loss of membrane ecto-ATPDase, contributing to platelet aggregation, C5a-induced loss of heparan sulphate, and exposure of foreign carbohydrates such as sulphatides which can activate the contact system of coagulation [1].

Summary of hyperacute rejection. Immediately upon revascularization of a discordant xenograft, complement activation begins on the surfaces of endothelial cells (Figure 9). Anaphylatoxins (C3a, C5a) are generated and act locally on basophils and mast cells to release histamine and cause degranulation of platelets, including serotonin. Within seconds, histamine and serotonin bind to receptors on endothelial cells, stimulate surface expression of PAF and P-selectin, and cell contraction. PAF causes a dramatic increase in vascular permeability and endothelial cells contraction, resulting in sludging of platelets and red blood cells within the microcirculation. Endothelial cell retraction exposes underlying vWF, basement membranes and collagen to plasma components, including platelets and the contact activator, Hageman factor. Together, these events result in stasis, platelet aggregation, and interstitial hemorrhages, which rapidly reduce compliance, such that a vascularized xenograft typically fails within minutes of engraftment. However, in some cases, grafts survive for a few hours such that neutrophil accumulation occurs in response to intragraft generation of chemotactic factor such as C3a and C5a.

Overcoming Hyperacute Rejection

Given the complex involvement of antibody, complement, coagulation and other inflammatory pathways in mediation of xenograft rejection, identification of the key events which are of therapeutic significance is clearly essential. XNA depletion (Figure 10), through combinations of splenectomy, plasmapheresis, absorption with soluble trisaccharides, organ perfusion and additional anti-B cell-directed immunosuppression has shown the important role of antibody in development of hyperacute rejection in the pig to primate combination. However, regardless of the protocol, antibody targeting has been incomplete, difficult to maintain and has at very best, prolonged xenograft in a handful of isolated cases from several hours to 14 – 15 days. Similarly, the effects of targeting the coagulation system alone, or inflammatory mediators such as PAF, though often resulting in statis-

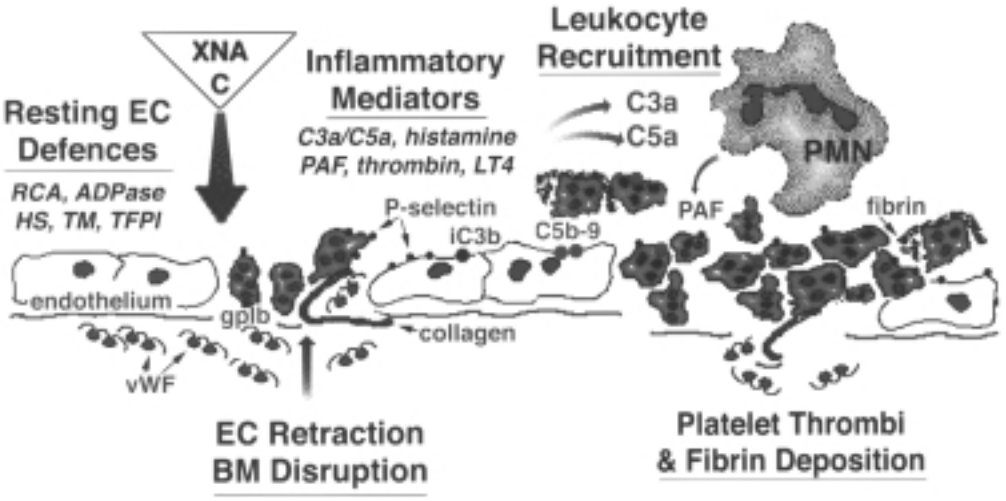

Figure 9. Model of hyperacute rejection, showing key components. On the left are two "resting" endothelial cells serving to maintain a barrier between the intravascular space and organ parenchyma. Endothelial cells normally express several proteins with anti-thrombotic actions, including thrombomodulin (TM), anti-thrombin III, tissue factor pathway inhibitor (TFPI), and the ectoenzyme ATPDase, which efficiently degrades platelet-derived ADP, thus inhibiting amplification pathways which result in platelet plug formation. Heparan sulphate on the endothelial cells also binds superoxide dismutase which degrades reactive oxygen species. Recipient XNA and complement activate porcine endothelial cells, leading to their retraction and development of interstitial hemorrhages. In addition, exposure of subendothelial molecules such as von Willebrand factor (vWF) allows adhesion and spreading of platelets, through the interaction of platelet receptor GP1b with vWF. The activation of platelets, with increased expression of P-selectin (also on endothelial cells) and GPIIbIIIa, is accompanied by release of inflammatory mediators, including platelet activating factor (PAF), thrombin and the leukotrienes (e.g. LTB4). The loss of ADPase activity with EC activation permits ADP to accumulate, which promotes platelet aggregation, leading to platelet thrombi. Fibrin is deposited consequent to loss of molecules from the surface of the activated EC that normally maintain anticoagulation, and the interaction of fibrin(ogen) with the GPIIbIIIa receptor on the activated platelets.

tically significant effects compared to controls (e.g. up to a few hours prolongation of graft survival), are not biologically meaningful.

The distillation of much data is that for the pig → primate combination, complement is by far the most effective therapeutic target, but the blocking of complement is itself not sufficient to achieve significant long-term survival (greater than a few days). Targeting the complement pathway using cobra venom factor or one of several alternate agents, such as soluble complement receptor type I (sCR1), FUT-175 or K76COOH, is about equally effective as, but more reproducible than, targeting of XNA, typically providing several days of survival, though there are important limitations. The toxicity associated with use of agents such as cobra venom factor renders them unsuitable for clinical usage, not to mention extremely expensive and prone to eliciting neutralizing antibodies. Hence, with the realization that the arcane world of complement includes multiple regulators of complement activation (RCA) (Table 1, Figure 5), and that such RCA are species-specific (Figure 11), genetic approaches to manipulation of the organ donor have received great attention. The main human RCA are CD46 (membrane cofactor protein) and CD55 which regulate expression of C3 convertase, and CD59 (homologous restriction factor) which blocks

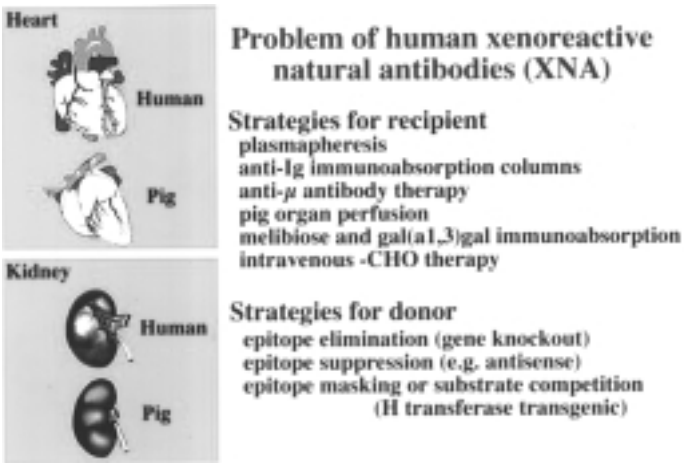

Figure 10. Approaches to the problem of circulating preformed XNA in patients about to receive a pig xenograft; unfortunately, none result in more than short-term XNA depletion or prolongation of survival, and are in the case of strategies for the recipient, are frequently associated with rebound to higher than normal XNA levels.

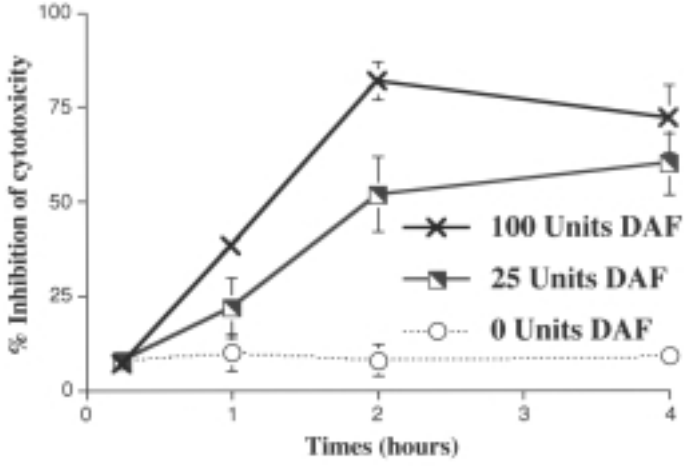

Figure 11. Human complement regulatory proteins such as decay accelerating factor (DAF, CD55) are species-specific. Their expression by pig endothelial cells in vitro protects the cells from lysis by human antibody plus complement.

insertion of C9 into the developing membrane attack complex of complement. Pig endothelial cells transfected with any one of these 3 main human RCA molecules show dramatically increased resistance to complement-mediated lysis in the presence of human serum (Figure 12), but the key point has to been to develop transgenic pigs expressing human RCA and test this approach in vivo (Figure 13).

In late 1992, Astrid, the world's first transgenic pig was born. Astrid was heterozygous for human CD55 and became the founder pig of a large herd at Cambridge University. In initial studies, in contrast to normal controls which reject within minutes to a few hours, organs (heart or kidney) from pigs heterozygous for human RCA such as CD55, when transplanted into unmodified baboon recipients, survived about 5 days (120 hours); grafts from homozygous donors survived about 130 hours [34]. Hence, expression of human RCA on pig endothelial cells can abrogate hyperacute rejection following xenotransplantation. Though initial pigs transgenic for CD55 had unpredictable and often low tissue expression, the application of new vectors now allows adequate expression of this transgene in the endothelium of pigs. In particular, the use of mini-genes which include at least one intron and whose expression is driven by the

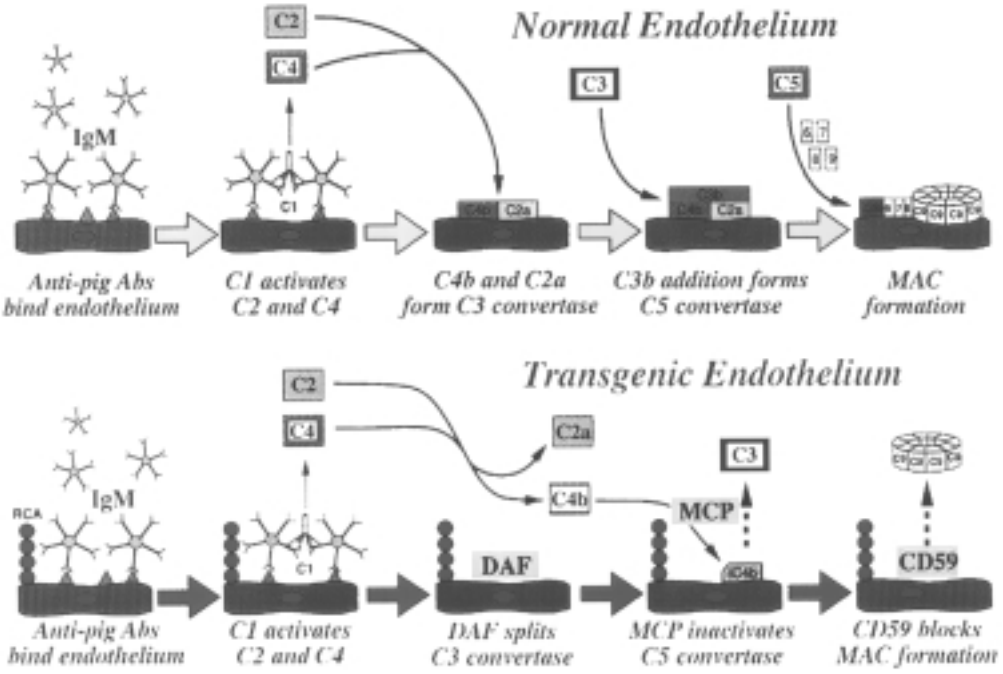

Figure 12. All species express cell surface proteins which serve as regulators of complement activation (RCA), acting to limit or suppress complement activation on the surfaces of autologous cells. RCA of particular interest to the development of transgenic pigs for clinical xenografting are human DAF, membrane cofactor protein (MCP, CD46) and membrane attack complex inhibitor (CD59), which act as shown.

human CD55 promoter has proven very successful. Markedly beneficial effects of addition of immunosuppression to xenograft survival, when pig donors transgenic for one or other human RCA are employed, are controversial; results in the small numbers of such xenografts known to have occurred are considered in the next section.

Delayed Xenograft Rejection

If hyperacute rejection is avoided by depleting XNA or complement, xenografts are rejected in days instead of minutes to hours, by a syndrome referred to as delayed xenograft rejection (DXR) [2, 5] (Figure 14), which is characterized by progressive infiltration over several days of mononuclear cells, primarily monocytes and natural killer (NK) cells, development of focal infarcts and interstitial hemorrhages, widespread activation of coagulation within the microvasculature and cessation of graft function.

DXR may appear an uninformative term when compared to terms such as hyperacute, acute or chronic rejection, which have clearly associated morphologic and immunopathogenetic features, leading some to also use the acute vascular rejection. However, large vessels in DXR are typically uninvolved such that its description as vascular rejection is a misnomer, and labeling the process as cellular rejection conjures up T cells, whereas such

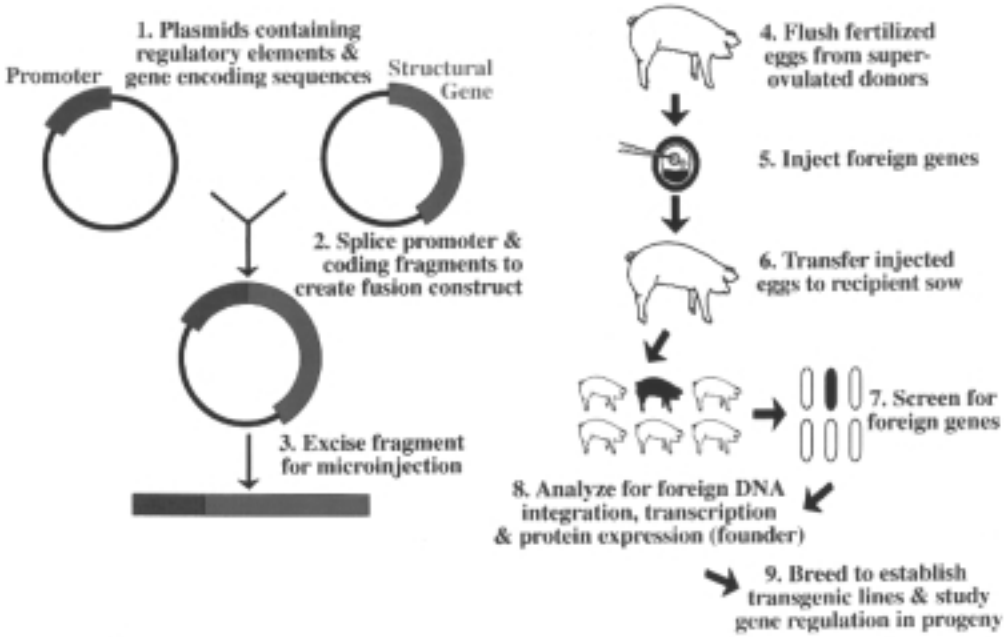

Figure 13. Sequential steps involved in development of a transgenic pig suitable for use in clinical xenografting.

cells are not necessary for DXR to occur [6]. Hence, DXR merely indicates the typical timing of discordant xenograft rejection in recipients which are, in effect, de-complemented, whether through use of cobra venom factor or analogous agent, or through use of donors expressing RCA, but otherwise unmodified. It is important to remember that hyperacute rejection and DXR represent parts of a continuum. Some of the components of hyperacute rejection, such as platelet activation or immunoglobulin deposition, do not typically result in hyperacute rejection if complement activation is avoided, and yet these responses, as well as activation of coagulation and endothelial cell responses, may contribute to development of DXR.

Platelets, P-selectin and Early Chemokine Expression

Mediators generated by the binding of residual antibodies and complement components, or as a result of ischemia and reperfusion injury include PAF and membrane expression of P-selectin. While use of a PAF antagonist prolongs cardiac xenograft survival in the guinea pig → rat model by 2 – 3 hours (compared to rejection in < 15 min in untreated controls), and administration of an anti-P-selectin antibody prolongs survival by only 30 – 60 min, their combined use prolongs survival for up to 18 hours [10], indicating the importance of pathways additional to antibody and complement in discordant xenotransplantation.

P-selectin translocation from cytoplasmic granules to the cell surfaces of platelets and endothelial cells occurs within a few minutes

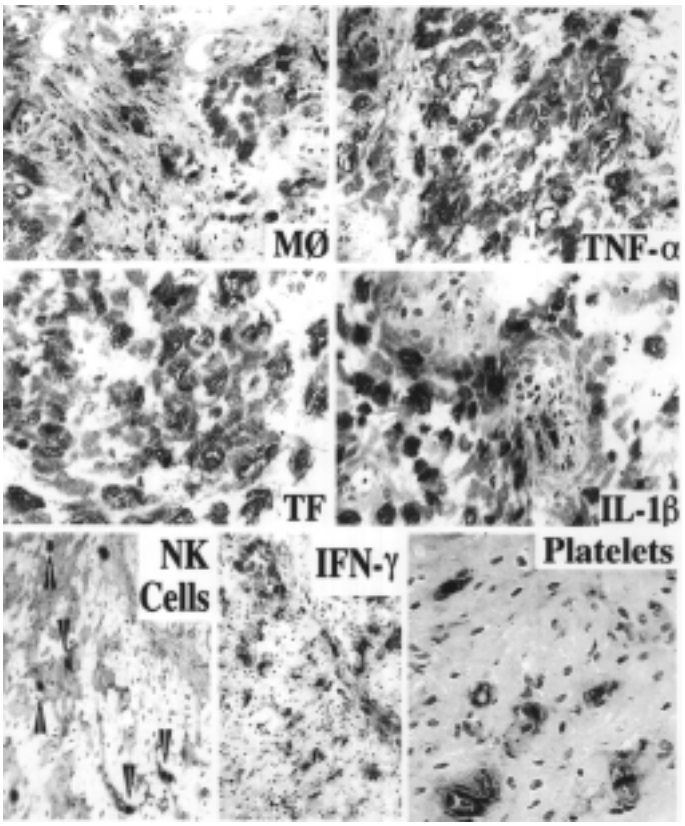

Figure 14. Immunopathology of DXR in a pig cardiac xenograft at day 5 post-transplant in decomplemented primate recipient, showing dense macrophage (Mϕ) infiltration plus lesser numbers of NK cells, along with examples of their respective cytokine products, such as TNF-α, IL-1β, and IFN-γ. Macrophages (and endothelial cells) show induction of the procoagulant, tissue factor (TF), and the microvasculature is associated with widespread platelet microthrombi. DXR can be accompanied by significant numbers of T cells, but at least experimentally can readily occur in T cell-deficient recipients (Cryostat sections, immunoperoxidase).

of xenografting [5], as result of the binding of antibody to endothelial cells and C1q deposition, or platelet aggregation induced by the actions of mediators such as PAF or histamine. P-selectin expression is important as an initial nidus for the attachment of inflammatory cells, especially monocytes, and it is known that monocytes are stimulated by their binding to P-selectin to produce C-C-type chemokines [9], as well as the procoagulant molecule, tissue factor [13].

The same α granules in platelets that contain preformed P-selectin, also contain the chemokines, monocyte chemoattractant protein-3 (MCP-3) and regulated-and-normally-T-cell-expressed-and-secreted (RANTES) [31], such that almost from the time of transplantation, as small numbers of platelets begin to aggregate and form platelet microthrombi within the microvasculature, sites for recruitment and activation of host inflammatory cells are created (Figure 15). Consistent with this, inhibition of platelet aggregation by treatment of the recipient with an antagonist to the platelet receptor, GP IIb/IIIa, prolongs graft survival in the guinea pig → rat model of DXR beyond that achieved by use of cobra venom factor (CVF) alone, and such grafts show somewhat decreased cellular infiltration especially during the initial 24 – 48 hours [7]. However, inhibition of platelet aggregation delays but does not prevent leukocyte recruitment, and, indeed, serial studies show that monocyte accumulation can be detected within a few hours of engraftment, in association with progressive expression of the

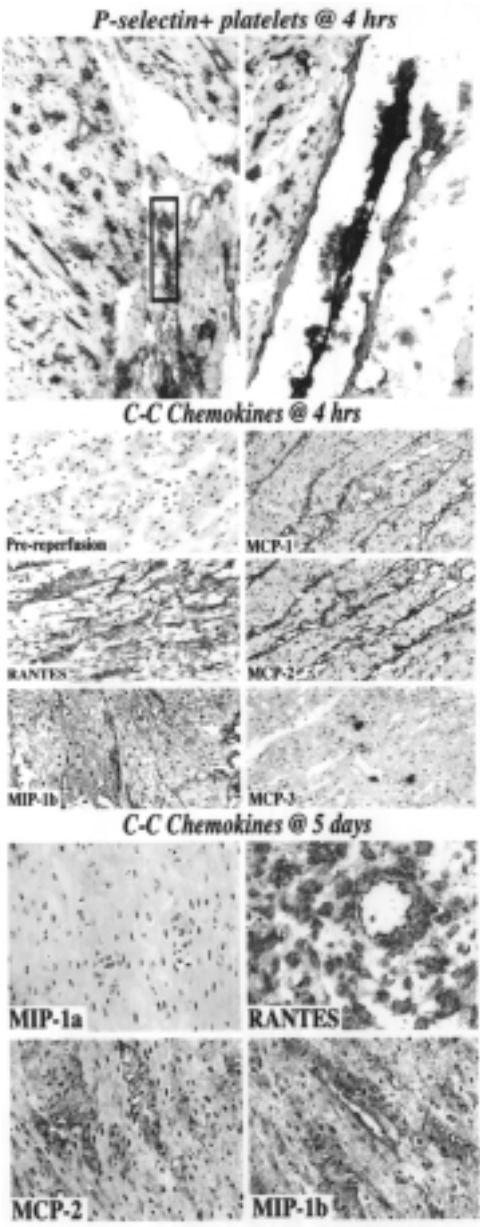

Figure 15. DXR and thrombosis of the vasculature are multicellular processes. Thrombosis takes place based both on events that are a part of type I activation, and on the expression of tissue factor (TF) by infiltrating macrophages and graft endothelial cells in decomplemented recipients. Platelet aggregates form based on the mechanisms already discussed in the text, and exhibit P-selectin expression; the boxed area (upper left) is shown at high power in the upper right panel, wherein macrophages are seen adherent to P-selectin+ platelet microthrombi. Multiple chemokines, as shown, produced by activated endothelial cells and platelets recruit (and then activate) leukocytes over succeeding days post-transplant (Cryostat sections, immunoperoxidase).

chemokines, MCP-1, MCP-2, MIP-1β and RANTES by intragraft monocytes and endothelial cells [19], presumably as a result of additional mechanisms considered later. Though no data are available concerning the effects of targeting of chemokines in the context of xenotransplantation, the multiplicity of chemokines produced and their overlapping specificities suggests that the inhibition of cell recruitment by use of antibodies directed against individual chemokines will likely be unsuccessful. However, the targeting of shared chemokine receptors through use of soluble antagonists or antibodies appears a more attractive option for future evaluation.

Insights into the mechanisms of platelet aggregation during the early post-transplant period, leading to local release of chemokines and providing a site for attachment of inflammatory cells, as discussed in the preceding paragraph, would allow development of therapeutic approaches to influence the course of DXR. Resting endothelial cells inhibit platelet aggregation, through their ability to break down the adenosine nucleotide ADP, a powerful agonist for platelet aggregation, as a result of endothelial membrane expression of the enzyme, ecto-ATPDase. However, endothelial cells subjected to oxidative stress lose ATPDase activity and become permissive for platelet aggregation, both in vitro and in vivo [33] (Figure 6). High levels of ATP and ADP also promote release of oxygen radicals from neutrophils resulting in an impor-

tant feed-back loop. Reconstitution of ATPDase activity by administration of a soluble apyrase prevents platelet aggregation within the microvasculature and prolongs xenograft survival by 50% over that achieved using CVF alone in the guinea pig → rat cardiac xenograft model [23].

Monocytes and NK Cells in DXR

Monocyte infiltration is one of the earliest features of developing DXR, beginning within 4 – 6 hours of engraftment and continuing until eventual rejection occurs [5]. Monocyte recruitment in decomplemented xenograft recipients appears to be largely complement-independent, although early complement components which are still present in CVF-treated hosts can be activated by xenoantibody binding to graft endothelial cells, e.g. C1q and C4b, and may contribute to monocyte activation to a modest extent. Monocyte recruitment during DXR may result from several additional mechanisms: binding to deposited xenoantibody through monocyte expression of Fc receptors fro IgG; the action of chemokines, especially those of the C-C family; and novel lectin-dependent interactions. There are no data as to the effects of Fc receptor blockade in xenograft models, so the role of Fc receptor-dependent recruitment remains speculative. However, in the guinea pig → rat model of DXR, reduction and maintenance of rat anti-guinea pig xenoreactive antibodies, as measured by flow cytometry and enzyme-linked immunosorbent assay (ELISA), does not appreciably affect the rate or extent of monocyte recruitment, or the tempo of rejection [22]. Intragraft expression of multiple C-C chemokines (Figure 15), including MCP-1 and RANTES, is known to occur in both pig → primate and rodent models of DXR [19, 22]. These chemokines are of potentially great importance since they can be produced by both macrophages and endothelial cells upon exposure to multiple stimuli, including hypoxia, thrombin, cytokines and direct cell stimulation, and both recruit and activate monocytes and NK cells, but their actual role during the development of DXR in vivo remains as yet ill-defined.

The third main mechanism for complement-independent attraction of host monocytes to a discordant xenograft involves unique proteins which recognize carbohydrate sequences on donor endothelial cells, as shown by induction of macrophage lectin during DXR in the guinea pig → rat model [22] (Figure 16). Using a monoclonal antibody to the carboxy terminus of the recently cloned galactose/N-acetylgalactosamine-specific macrophage lectin, 80% of inflammatory monocytes which accumulated rapidly following xenografting were shown to express the lectin, whereas negligible induction was seen during development of acute rat cardiac allograft rejection. Moreover, macrophage lectin was induced on rat monocytes by exposure to xenogeneic cells in vitro, and induction was not suppressed by the addition of deoxyspergualin or leflunomide. Macrophage lectin is a C-type (Ca2+-dependent) macrophage-specific lectin, and one of a family of type II transmembrane proteins that also encompasses the collectins and receptors on NK cells, including NKR-P1 (see below). C-type lectins each contain a single COOH-terminal carbohydrate-recognition domain (~130 amino acids long), and differing domains have specificities for various different saccharides.

Macrophage lectin messenger RNA (mRNA) is absent from resting cells, and is known to be induced by 24 hours of exposure to Con-A conditioned medium but not standard monocyte-activating stimuli such as inter-

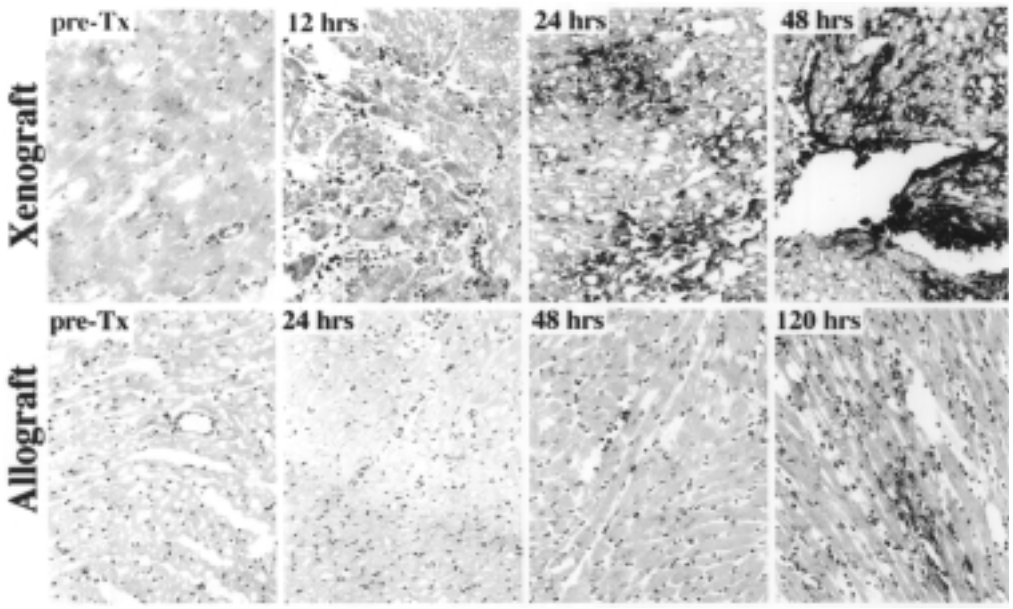

Figure 16. Xenografts induce recipient macrophage activation and surface production of a lectin whose expression can promote macrophage infiltration during DXR, independent of other mechanisms including immune adherence or chemokine action; this induction is observed to only a minor extent in corresponding rat cardiac allografts (Cryostat sections, immunoperoxidase).

feron-γ, Lipopolysaccharide (LPS), interleukins IL-2, IL-4 or IL-6, nor by complement components generated during the initial phase of therapy with CVF. Once expressed, macrophage lectin can mediate the direct binding to, and killing of, various target cells by Mϕ. Hence, Mϕ lectin induction upon exposure to xenogeneic cells may provide a potent means for the rapid recruitment and activation of host macrophages to the vascularized xenograft, as a result of macrophage recognition, adhesion and infiltration of xenogeneic tissue expressing as yet undefined carbohydrate ligands. While macrophage depletion is notoriously difficult, unreliable, and likely to lead to an immunodeficient state, selective targeting of macrophage lectin with neutralizing monoclonal antibodies, peptide inhibitors or administration of specific sugars to saturate the membrane molecule, may provide a new and specific approach to blocking macrophage infiltration, activation and subsequent cytokine production during development of DXR. In addition, analysis of macrophage lectin transcripts or protein expression in biopsy or other tissue samples could prove of use in consideration of the mechanisms of action of new therapeutic agents with possible macrophage-directed actions, or in the monitoring of macrophage-dependent mechanisms of xenograft rejection.

Similarly to macrophage lectin, NK cells express lectins of likely importance to the pathogenesis of DXR. In particular, rat NK cells infiltrate guinea pig xenografts during DXR [5], as shown using the 3.2.3 monoclonal antibody which recognizes the NKR-P1 antigen, a C-type lectin that is related to the NKG2 molecule of human NK cells. In vitro studies of NKG2 indicate that the lectin

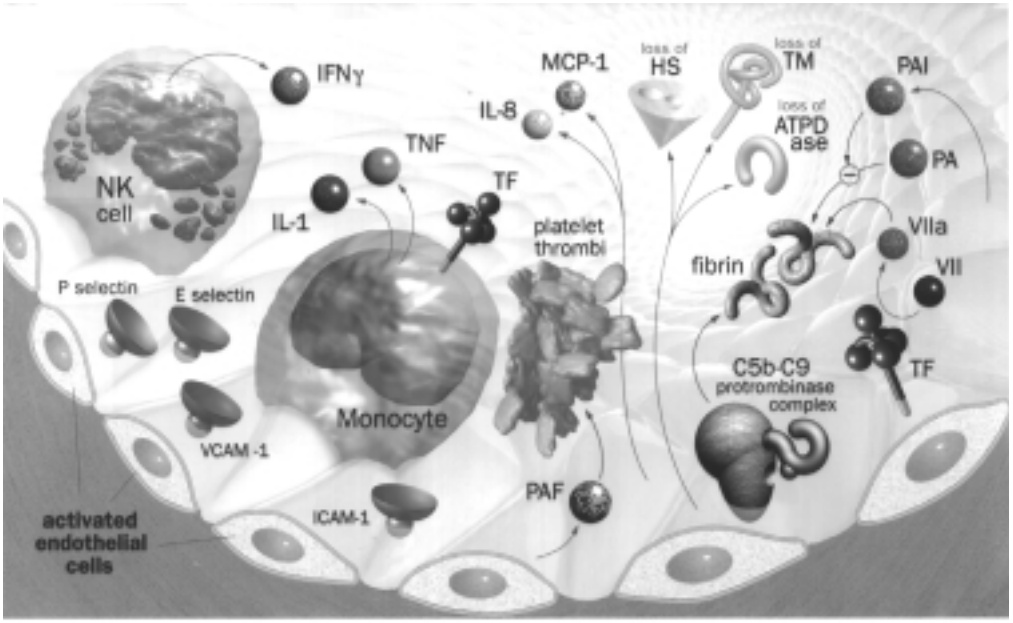

Figure 17. Diagram of events during DXR, focusing on endothelial/leukocyte interactions, as discussed in the text.

recognizes some of the same sugar moieties as those detected by human xenoreactive antibodies. Hence, NK cells in various species express de novo membrane receptors which facilitate their binding to donor endothelial cells.

Endothelial Responses During DXR

Analysis of serial samples from small and large animal models has demonstrated considerable evidence of endothelial cell activation during discordant xenograft rejection (Figure 17). Endothelial responses include the following:

– shift to a procoagulant state, with down-regulation of surface thrombomodulin and induction of tissue factor, consistent with dense local fibrin deposition;
– induction of leukocyte adhesion molecules, including, progressively, E-selectin and ICAM-1; and
– production of chemokines such as MCP-1, as well as other cytokines.

Once present within discordant xenografts, macrophages [29] and NK cells [16] can bind directly to, and activate, donor endothelial cells; activation is also facilitated by production of multiple cytokines by these two cell types, including IL-1β, tumor necrosis factor-α (TNF-α) and interferon-γ. It is likely that such activation amplifies the inflammatory responses inherent to DXR through still further induction of leukocyte adhesion molecules, production of chemokines and upregulation of target xenoantigens, but the extent to which DXR can occur in the absence of any host leukocyte responses remains unknown. It is conceivable that with reperfusion or other

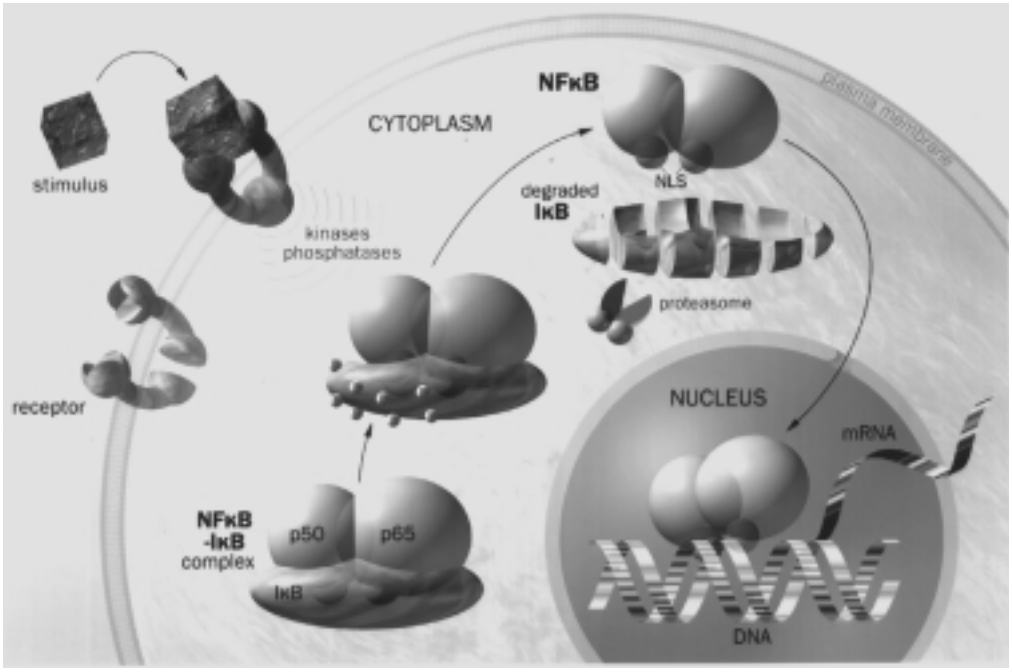

Figure 18. Diagram of the events involved in activation of cytoplasmic NFκB, dissociation from IκB, exposure of the nuclear localizing sequence (NLS) and translocation to the nucleus where many pro-inflammatory genes are activated. Examples of relevant NFκB-dependent genes include those encoding adhesion molecules (E-selectin, ICAM-1, VCAM-1); cytokines and chemokines (IL-1α, IL-1β, IL-2, IL-6, IL-8, TNF-α, TNF-β, IFN-β, IFN-γ, MCP-1, Gro-α, RANTES, PDGF, G-CSF, M-CSF, GM-CSF, LIF) membrane receptors (MHC class I (H-2K^b) and class II (Ea^d), β2 microglobulin, Ig kappa chain, TCR-α/β, IL-2R) and molecules associated with endothelial and smooth muscle cell function (iNOS, leukotriene B4, prostaglandin-E, tissue factor and urokinase-type plamsminogen activator).

injury to the endothelium, graft endothelial cells may retract from one another, exposing the adjacent subendothelial matrix. Several adhesion proteins which are in the subendothelial matrix, including collagen and vWF, can interact with platelet adhesion receptors, such as integrins and GPIb, and thereby trigger activation of the platelets. Once activated, platelets can express and secrete chemokines as described above, as well as contributing to thrombin generation and fibrin formation. Thus, endothelial responses independent of host leukocyte recruitment might lead to xenograft rejection, particularly through the activation of host platelets and subsequent widespread endothelial cell fibrin deposition. However, since anti-platelet or specific anticoagulant therapies have only a modest or no effect on the tempo of DXR, the importance of leukocyte recruitment appears likely. Lastly, while effective macrophage depletion is difficult to achieve in vivo, transfer of macrophages from rat recipients of a first xenograft to a CVF-treated naive rat accelerates the rejection of a discordant xenograft of the same donor species [14], further emphasizing the importance of host mononuclear cell responses.

The overall significance of endothelial activation in DXR is controversial. On one hand, these are “down-stream” events which are present in essentially any inflammatory re-

Table 2. Genetic Manipulations of the Pig Organ Donor to Promote Xenotransplantation

Target	Concept	Comment	When?
Transgenic expression of human RCA	Expression of human CD46, CD55 or CD59 on pig cells will locally regulate assembly of complement cascade	Prevents HAR, but without additional massive immunosuppression xenografts reject in 4-5 days; alternate vectors to increase endothelial expression are being evaluated (e.g. CD55)	Testing underway
Transgenic expression of H-transferase	α1,2 fucosyltransferase overexpression may compete with endogenous α1,3 galactosyl transferase	May usefully be combined with pigs transgenic for RCA	1-2 years
Transgenic expression of inhibitors of endothelial activation	Regulated expression of IκB, a natural inhibitor of NFκB, or a dominant negative mutant of the NFκB subunit RelA, by endothelial cells	Strategy to inhibit NFκB, a key transcription factor essential for inducible gene expression in endothelial cells; regulation of inhibitor in vivo achieved through use of tetracycline-sensitive promoter	2-3 years
Yeast artificial chromosome (YAC) transfer of human genes	Large portions (~150-300 kb) of human chromosome carrying desired transgene	May be used to achieve position-independent expression of multiple human genes; in long term could be used to introduce human MHC genes into donor pig, creating "self-pig"	2-3 years
α1,3 galactosyl transferase deletion	Block pig expression of Gala 1,3Gal residues recognized by human XNA	Requires isolation of a pig stem cell line; other sugars may still bind XNA	2-3 years
Swine MHC (SLA) deletion	Block pig expression of pig MHC genes to facilitate tolerance induction	Requires isolation of a pig stem cell line; pig β2-microglobulin cloned so targeting of swine class I feasible; class II genes have very restricted expression and may be less important	2-3 years

sponse, albeit to a more florid extent than usual. On the other hand, the ability to genetically engineer the donor animal suggests the potential for modulating endothelial responses by genetic approaches, e.g. by regulated targeting of the nuclear factor-κB (NFκB)-dependent endothelial cell pathways (Figure 18, Table 2). Hence, a unifying concept for therapy of DXR is that that in lieu of dense T cell-directed immunosuppression, with additional targeting of complement, coagulation and host macrophage and NK cells, modulation at the graft level by such genetic approaches will be important to the development

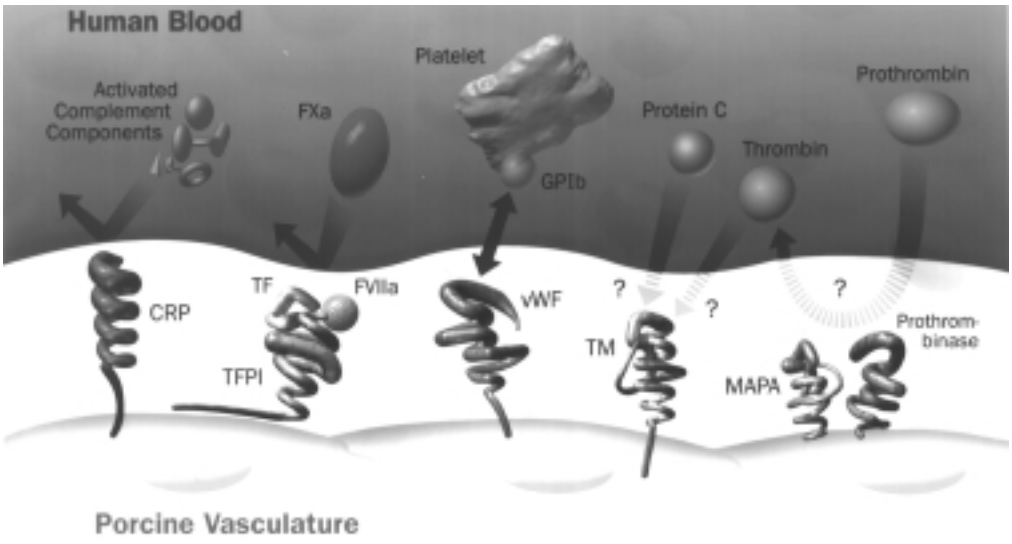

Figure 19. Summary of the myriad molecular incompatibilities which contribute to inflammation at the host/graft endothelial interface; these include lack of effective interactions of complement regulatory proteins (CRP), and multiple components of the coagulation pathway.

of clinical xenotransplantation as a practical solution to the lack of organ donors; testing in vivo in small animals is underway.

Molecular Incompatibilities and DXR

Earlier sections emphasized that many of the features of DXR reflect activation of innate host defense mechanisms. A key additional point, given that one could reasonably ask why is this so special in xenotransplantation, is that DXR occurs as part of the failure of normal regulatory mechanisms due to manifold xenogeneic molecular incompatibilities (Figure 19).

Proteins that interact in a given manner within an individual, or following allografting, may interact only poorly or not at all when present in a xenogeneic combination. Well-known examples of minimal or no effective interactions include membrane-associated inhibitors of complement such as decay accelerating factor (DAF), as well as other regulators of complement activation, but there are many other relevant instances. Molecules which regulate local platelet aggregation at the endothelial cell surface, such as ecto-ATPDase are rapidly lost post-xenografting and/or are ineffectual across species. Regulators of coagulation such as thrombomodulin are downregulated by local cytokine production during DXR [5], and even in the quiescent state in vitro, pig thrombomodulin does not efficiently activate human protein C to activated protein C [21]. The latter incompatibility may have further important implications favoring the development of monocyte activation and DXR, since activated protein C is a physiologic anti-inflammatory agent which normally serves to limit and downregulate monocyte activation [21]. Tissue factor pathway inhibitor (TFPI), which inhibits human factor X and the TF-VIIa complex of the

coagulation cascade by the formation of a quaternary complex in a factor Xa-dependent manner, is only weakly active in the pig → primate combination [25], again favoring coagulation within the vasculature post-xenografting. Lastly, the molecular incompatibility can change the conditions under which a given reaction takes place. Interaction of human vWF with human GPIb leads to activation of the platelets, though only in the presence of shear stress. Porcine vWF can also interact with human GPIb, but in contrast can lead to platelet aggregation without shear stress as would occur in von Willebrand disease. Thus, molecular 'incompatibilities' can initiate reactions that might ordinarily not take place but do so in xenogeneic combinations.

Unforeseen Consequences of Transgenes

The development of pigs transgenic for human proteins may, unexpectedly, actually facilitate development of DXR [17]. Recent data show that CD55 is a high-affinity ligand for the seven-span transmembrane molecule, CD97, which is rapidly expressed upon activation of many leukocytes, but particularly monocytes and NK cells. Hence, genetic engineering of pig organs to express human CD55, although abrogating hyperacute rejection, may itself predispose to development of DXR. Similarly, other groups have engineered pigs transgenic for the regulator of complement activation, CD59, which may enhance T cell responses to the graft since, like ICAM-1/CD58, CD59 is a ligand for the CD2 pan-T cell antigen. Thus, although DXR can occur in the complete absence of T cells (4), their presence almost certainly facilitates xenograft rejection.

Summary of DXR

Once hyperacute rejection is overcome, xenografts show progressive mononuclear and endothelial cell activation, cytokine expression, platelet and fibrin deposition, and rejection within a few days. Logically, DXR may be caused by

- infiltrating mononuclear cells;
- consequences of EC activation; or
- a combination of both.

NK cells could be present secondary to direct "recognition" of xenogeneic endothelial cells, and either cell type could be present through Fc receptor binding of IgG bound to endothelial cells, lectin interactions, or chemokine production. Aspects of direct binding and activation of endothelial cells by macrophages and NK cells have recently been described. Once present and activated, mononuclear cell products, including cytokines and tissue factor, contribute to coagulation, damage surrounding endothelial cells and depress myocardial contractility. The factors that result in activation of endothelium in DXR are not well defined. XNA binding to pig endothelial cells in vitro causes upregulation of IL-1, IL-8 and plasminogen activator inhibitor-1 (PAI-1), though the in vivo relevance of these findings is not established. Following stimulation, activated endothelial cells contribute to inflammation and thrombosis.

Potential Therapeutic Approaches to Control of DXR

Given the multiple pathways involved in development of DXR, the choices for therapy are:

- multiple therapies each of which is directed against one of the pathways identified to date;

– blanket immunosuppression in an attempt to complete obliterate deleterious host responses; and
– genetic engineering to regulate donor endothelial responses such that the toxic effects of cells, cytokines and other mediators might be diminished.

It is premature to favor any one of these choices as yet, though blanket immunosuppression as outlined in the introduction has hitherto been relatively unsuccessful.

The key features of DXR which lead to, but precede, endothelial cell activation in DXR, include the recruitment and activation of host monocytes and NK cells. These cell types exhibit multiple, cytokine-dependent interactions and, if xenografts are not already rejected, can facilitate host T and B cell responses. Understanding the mechanisms for their recruitment is essential, but likely approaches for therapy include strategies to block lectin interactions with graft endothelial cells. While in the long-term, knockout or decreased expression of the galactosyl transferase gene may decrease NK cell response, given their likely recognition of gal(α1,3)gal sequences, this will not affect monocyte activation. Moreover, activated monocytes can produce CC chemokines which will recruit NK cells, independently of NK cell-expressed lectins. Hence, targeting of platelet aggregation and host monocyte responses, i.e. the earliest events in development of DXR, are essential. Likely, based upon preceding sections, therapeutic approaches include the combination of PAF antagonists, soluble sugars or anti-macrophage lectin monoclonal antibody to block the function of macrophage lectin, and agents which will regulate macrophage activation as well as coagulation. In the latter case, use of activated protein C may serve both functions, and indeed such studies are underway in rodent models [21].

Preliminary data indicate that such multifaceted therapies may not necessarily need to be maintained long-term, since induction of regulatory T cell responses and protective genes within endothelial cells appears to occur which together lead to prolonged survival, at least in concordant models, of cardiac xenografts with only minimal maintenance therapy [3, 4]. In the latter studies, prolonged concordant xenograft survival was associated with induction of "protective" genes in graft endothelial and smooth muscle cells; these genes include Bcl-2 and Bcl-xL, A20 and heme oxygenase, and are notable since, at least in vitro, expression of these genes in endothelial cells provides potent anti-apoptotic effects as well as resistance to NFκB activation [3, 4, 20].

Genetic engineering, using endothelial-specific promoters such as intercellular adhesions molecule-2 (ICAM-2), of graft endothelial cells to control endothelial cell activation during DXR will likely involve the targeting of NFκB-dependent pathways, and would be ideally be undertaken in conjunction with expression of human RCA molecules and possibly H-transferase. Many potential transgenes, including use of the "protective" genes listed above, might be considered for use so as to alter the balance from endothelial activation towards a quiescent state post-xenografting (Figure 20). However, given the important role of many NFκB-dependent genes (Table 2) in endothelial cell function, expression of an NFκB-inhibitory gene in a regulated fashion would be desirable, and there is preliminary data that this is feasible [20] (Figure 21).

T Cell Responses

Studies from many groups over the past few years have led to considerable advances in our

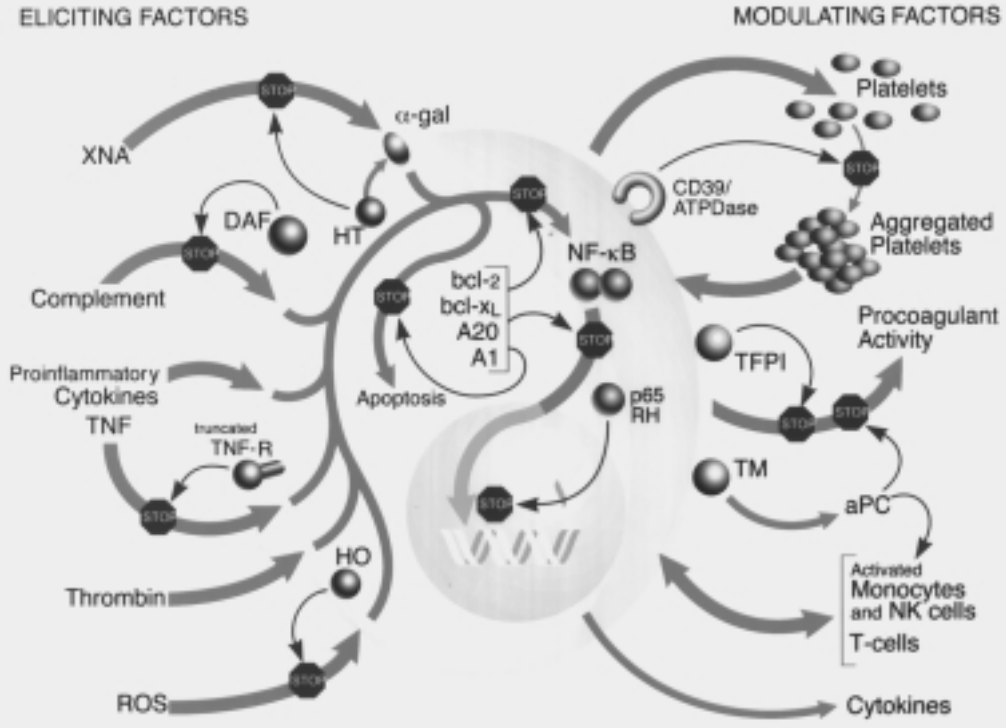

Figure 20. Diagram of factors at the endothelial level which elicit vs. modulate endothelial cell activation following xenotransplantation. Agents shown in gold can inhibit the pathways indicated and represent likely future approaches to control of DXR via their tissue-specific expression in transgenic pigs.

knowledge of xenotransplantation. The concept of DXR, involving a greater understanding of the mechanisms that contribute to inflammation and thrombosis, and appreciation of molecular incompatibilities, has begun to lead to new approaches to therapy. It is clear that as the problems of hyperacute rejection, and eventually DXR, are overcome, host T cell responses will need to be tackled. Many assume that this will simply involve using the T cell-directed therapies currently used in the context of allotransplantation, but this is not by no means proven. A logical approach will be to develop approaches to overcome DXR without predisposing to subsequent enhanced cellular responses in the way that use of certain transgenes overcome hyperacute rejection but predisposes to DXR. Similarly, the ability to engineer the donor suggests that strategies to induce tolerance may play a role in achieving long-term xenograft survival, but hard data are lacking.

Biocompatibility

Though xenotransplantation has a long and fascinating history, in the modern era studies of xenograft biology and especially xenograft rejection can be simply divided into the transgenic and pre-transgenic phases. This is because the option of engineering a xenograft to decrease its immunogenicity, and prolong its survival and adequate function, is profound in

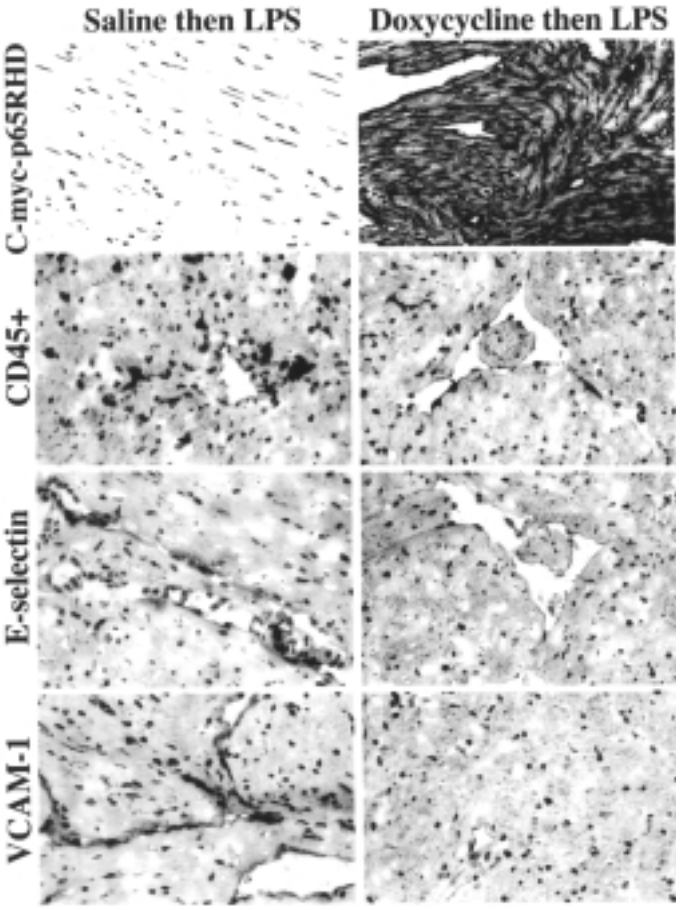

Figure 21. Tetracycline-regulated expression of a dominant-negative inhibitor of NFκB, termed p65RHD, under control of an ICAM-2 promoter. Left panels show how hearts from control mice lack expression of p65RHD and upon injection of lipopolysaccharide show recruitment of CD45+ leukocytes in conjunction with induction of E-selectin and VCAM-1. Right panels show how doxycycline therapy induces p65RHD and protects mice against LPS-associated NFκB activation, endothelial activation and leukocyte recruitment. This approach may be used, in conjunction with oral tetracycline therapy, to control intragraft endothelial cell activation of NFκB-dependent pathways in a pig xenograft.

its consequences for the transplant community, and, by extension, to the broad field of medicine. Faced with the almost evangelical fervor of proponents of xenotransplantation advocating immediate clinical trials of organs from the currently available transgenic pigs, plus awareness of the crisis in organ donation rates vs. numbers of patients, it is important to ponder for a second the things we do not yet know. None of the trials of very small numbers of pig to primate xenografts have yet addressed issues of biocompatibility.

Indeed, no data on the basic physiology of pig organ function following xenografting are yet known, nor more subtle factors such as hormone production and compatibility (e.g. pig and human erythropoietin show only about 80% amino acid identity, and vasopressin function was inactive in rat recipients of hamster kidney, leading to very large urine volumes); ability to grow in the host (will human growth hormone cause unrestricted growth of a pig xenograft?); hemodynamic factors (effect of gravity and differences in blood volume and pressure) and, as occurred in early studies using chimpanzee donors, the potential for rapid development of chronic rejection. The coming years are likely to see far more attention paid to such issues, as well as establishment of pathogen-free colonies, before clinical trials are seriously considered worthwhile.

Economics of Xenotransplantation

Review of the economics of establishing clinical xenotransplantation is warranted given that xenotransplantation has the potential to completely swamp existing transplant programs and render allotransplantation a minor component of organ grafts performed clinically. Such a perspective is timely since the main constraints on the growth of organ transplantation as a clinical option are donor supply and the very practical matter for the health system and the patient of the costs of the procedure, including hospitalization and maintenance immunosuppression (~$4,000/year for cyclosporine alone). Advocates of transplantation have frequently pointed out the financial benefits of organ transplantation over other options, e.g. kidney allografting vs. maintenance dialysis for those with end stage renal failure. Full-scale use of transplantation as a widely available therapy, however, has never really been openly discussed until now when the baby-boomers are coming of age (someone turns 50 years of age every seven seconds in the U.S.), the economy is robust and the scientific and business communities are reaching hitherto unprecedented degrees of interdependency and cohesion.

The Argument for Development of Xenotransplantation as a Clinical Modality

Peter Laing of the Salomon Brothers investment group recently published a detailed report [26] on the market implications for Sandoz (prior to its merger with Ciba Geigy to become Novartis) of the development of transgenic pigs. Laing views the results of initial xenografting of organs from transgenic pigs bearing human complement regulatory proteins into primates rather more rosily than almost any of the scientists in the field. In fact, Laing anticipated clinical trials to begin in 1996 and regulatory approval to begin in 2000. Events in both the UK and here, including the reports of government inquiries, have slowed the tempo of such developments largely due to the fear of transfer of pathogenic viruses or other agents, as noted in submissions by various groups to the regulatory hearings in the U.S. However, the implications of xenotransplantation for the estimated 700 transplant centers worldwide performing about 45,000 transplants/year will be summarized.

The introduction of xenografts would overcome the limited organ supply that currently restricts the rate of organ transplantation, especially since, Laing argues, transplants are cheaper and offer a superior quality of life than alternative therapies (issues such as the costs to society were not considered). This leads to a projection that the annual rate of transplants will rise 10-fold by 2010 (Figure 22). Since Novartis has major proprietary rights to much of the technology associated with development of such xenograft donors, the outcome to Sandoz could be over half of the $6 billion/year market in xenotransplantation anticipated by 2010. This would be enhanced by an anticipated $5 billion/year market for Sandimmune (currently about $1 billion annually), even after taking into account the loss of market share to generic formulations of cyclosporine and other immunosuppressive drugs; thus development of xenotransplantation as a clinical option, or indeed, conceivably as first choice for therapy in many cases, stands to dramatically enhance the income to pharmaceutical companies.

This is an extraordinary development. Consider the variety of chronic degenerative dis-

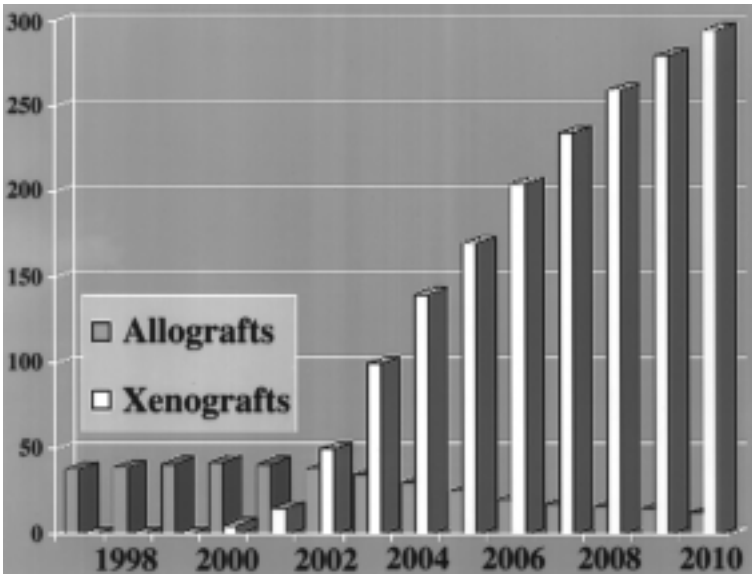

Figure 22. Projected worldwide rates of renal allografts vs. xenografts (shown as thousands of grafts/year).

eases that predominate as the main causes of organ failure, the demographic factors leading to substantial increases in the proportion of the elderly in industrialized countries and yet the proscription against those aged 55 – 65 years or more from entering waiting lists for transplantation. In essence, the market assessment is that these people and others should, and perhaps will all, be able to receive a well-functioning xenograft harvested under optimal conditions, engineered to minimize the host immune response while allowing elective transplantation as desired, followed by ongoing immunosuppression.

The Logistics of Xenotransplantation

Arguments in favor of the feasibility of clinical xenotransplantation necessarily require some data in support of its logistic aspects. The working model described by Laing is as follows. Production will likely begin based upon assuming one organ/transgenic pig and a demand, at the current rate, of about 50,000 transgenic pigs/year. A 100-sow breeding unit, with at least 2 litters/year, would generate at least 1,600 pigs/year (factoring in litter sizes of 10 – 11 and a 10% mortality rate), such that 30 such units could supply all of the current demand for organs worldwide. The costs of production assume indoor rearing units to cover pigs for the first 12 weeks after birth, followed by their transfer to separate indoor finishing units in which the animals grow to the desired weight of about 70 kg. These units are not large; together they would occupy ~16,000 square feet or 0.4 acres (smaller than most U.S. suburban blocks). Factoring in costs of these barrier facilities, including feed and labor costs, plus depreciation, direct or production costs would be about $765/organ. These estimated costs would likely double to about $1,580/organ when the indirect costs of surgical harvesting, quality control, organ delivery and carcass disposal are factored in to the assessment.

Laing anticipates Novartis might initially charge transplant centers $12,000/organ, on the basis of needing to recoup the costs of investment in research, and notes that this is

still well below the current cost of harvesting a human donor organ (~$15,000 – $18,000 in the US given intensive care unit (ICU) support for > 48 hours of the brain-dead donor and the operational costs to maintain a team for action at any hour of the day). Note that this and many other studies involving U.S. estimates of costs associated with organ transplantation are very high by European standards (perhaps 3 times that of European Union median costs), but reflect what U.S. hospitals charge for reimbursement rather than what the actual costs incurred may be.

Using the median (50th percentile) data and adjusted for 1997, "typical" breakdowns of the ~$46,000 for a kidney transplant would be $24,000 for hospital charges, $5,000 for surgeons' fees, $2,000 for other professional fees, and $15,000 for donor procurement fees. For a renal xenograft, presumably surgical and professional fees would be comparable, but donor procurement might initially cost $12,000, and hospital charges might be far less since for an allograft recipient these may encompass costs lessened by harvesting and transplanting under ideal conditions with minimal ischemia/reperfusion and arguably better immediate graft function. Even with a rather conservative one-third reduction in hospital charges, a renal xenograft might "cost" $36,000, a 20% savings for the hospital phase.

Moreover, when data from Gambro and Baxter on the growing numbers of patients on maintenance dialysis are considered, the anticipated 7-fold rise in the annual rate of transplants as a result of using pig donors causes the number of patients on dialysis to fall only slowly. For example, even with the advent of pig xenografts, the world-wide pool of patients on dialysis will fall only ~8%/year between 2005 and 2010. With an average cost of ~$25,000/year (U.S. figures), the annual treatment costs of patients on dialysis in 2010 would be > $15 billion. Laing estimates that the costs of pig xenografting will be $10 billion/year by 2010, and this market will by that stage have only barely begun to reduce the pool of dialysis patients. Clearly there are powerful market forces pushing in favor of xenotransplantation.

Such considerations could be expected to be markedly enhanced still further in favor of xenotransplantation if the costs associated with cardiac transplantation were substituted, given the frequent need for pre-transplant life support and expensive ICU facilities. Thus, Laing estimates a pig cardiac xenograft would cost ~$50,000 vs. $50,000 for a left ventricular assist device plus $60,000 for its surgical implantation. Moreover, with time, experience, economies of scale and the ability to harvest multiple organs from each pig once appropriate organization and distribution systems are established, will likely result in considerably lower production costs, though how far these will be passed on to the patient are hard to predict. Similarly, the extent to which maintenance immunosuppression and the frequency of rejection, infection and other complications will vary is unclear, though the companies, with few exceptions, are largely betting on ongoing immunosuppression being required.

Commercial Factors Inhibiting Development of Clinical Xenotransplantation

Pig farming is currently a big business, with over 90 million pigs killed each year in the US alone for food and other products. However, there are downsides in the late 1990s, which predictably has consideration of environmental impact as a major concern. There is currently a campaign in Kansas against cor-

porate pig farmers; < 0.1% of pig farmers produce > 20% of pigs (up to 50,000 pigs/farm), and there are major problems with waste which runs into holding pools and then seeps into the ground water supply. This has led even many of the previous supporters of the pig-farming industry to question its practices and worth in the modern era. Will this affect the development of transgenic pig facilities? Probably not in the very direct sense, but yes in the broader sense of public concerns about the environmental impact and logistics of intensive pig farming, whether destined for the kitchen or operating table.

Will mechanical cardiac assist devices, currently only approved for short-term use, diminish the market for pig xenografts? Arguably not because of the latter's better physiologic responses, lack of need for a power supply, decreased risk of thrombosis, lesser size and use in patients other than just those with left ventricular failure. Moreover, those in favor of xenografts point out that the procedure is not only cheaper than using mechanical devices, but may also eventually replace coronary bypass surgery and cardiac valve replacement. Perhaps the market, or indeed the health budget, will be the limiting factor after all. The U.S. currently spends about 14% of its gross domestic product on health costs which is higher than that of any other industrialized nation. Whether the nation will consider still further expenditures as a result of dramatically expanded use of transplantation as a therapeutic option is debatable. Despite the many arguments for the economy of xenografting compared to that of allotransplantation, fear of the economic impact of clinical xenotransplantation may well curtail the projected growth curves of xenograft-based services, and corresponding corporate profits, regardless of whether the basic scientists ensure that pig organs can ever be engineered to "fly".

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Subject Index